PEDIATRIC CLINICS OF NORTH AMERICA

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SYMPOSIUM ON CARE OF THE PREMATURE INFANT

FOREWORD

F. THOMAS MITCHELL, M.D.

The majority of prematures in our country are not in the few great premature centers. A wide dissemination of the available knowledge on premature care is therefore advisable so that methods and techniques may be improved for the prematures on small pediatric services and those in small general hospitals, as well as those managed in the home.

Medical literature previous to the middle of the last century contains few references to the premature baby, and no material on a particular system of management appears until much later. Since 1910, however, a large amount of writing on this subject has accumulated, and today one can easily find articles which deal with every phase of premature development and growth; physiology, including the handicaps imposed by premature delivery; the influences of heredity; malformations and injuries. Other publications dealing with every detail of premature care are available. As medical knowledge has encompassed the fields of the endocrines, vitamins, allergic reactions, chemotherapeutic and antibiotic agents, articles on all these in relation to their adaptation to premature care have appeared in the literature.

The premature baby, because of his immature development, requires attention from birth which must differ from that sufficient for the full term baby. A study of the application of these particular principles is separate from the regular pediatric knowledge which applies to full term and more vigorous babies, just as the practice of Pediatrics, because of the difference in the age of the patients concerned, imposes conditions altogether different or definitely modified from those met with in adult medicine.

Today, surrounded by modern care, the premature may occasionally suffer even a severe infection or undergo major surgery with recovery. The premature responds to the new drugs as does the larger baby, and the use

of these as a preventive measure has much lessened the incidence of infections which formerly were frequently fatal. The nurse particularly trained and skilled is necessary if complete advantage is to be taken of our present knowledge. These people are now being paid the recognition and respect which they have earned, and several nurses are recognized specialists and teachers in the field of premature nursing.

This collection of articles does not attempt to completely detail the modern care of the premature baby. A number of excellent books by outstanding authorities do this fully and perfectly. Rather, the contributors to this volume have tried to clarify some of the conditions observed and to provide particular and detailed information on some of the questions regarding the premature state and the management of the premature baby which are of interest to those engaged in this field of medicine. Some of the material presented is controversial, and some of it perhaps subject to adverse criticism in the opinion of a few authorities. All this is knowingly included to completely present as far as possible today's thinking on both old and new subjects relative to the premature.

Several methods of management are presented for some conditions. This is well, since each premature should be individually observed and studied as larger babies are. It may not be best for a practitioner or an institution to have a set or routine method for caring for any group of individuals or conditions. A practice more flexible and more individually adapted is better even in premature care. A collection of opinions which vary affords the reader opportunity to choose the method best suited to the particular patient and within the scope of available personnel, equipment and quarters.

The contributors to this volume were selected because of their recognized knowledge of the subjects requested. Each has presented an excellent treatise. I am deeply grateful to them for their willingness to cooperate, and I appreciate the time and effort which they devoted to bring this publication to its high level of interest and value.

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MATERNAL FACTORS IN PREMATURITY

EDITH L. POTTER, M.D.

Innumerable papers have been written on premature infants—on how to prevent premature birth, how to take care of prematures after they have been born, and why they die. Prematurity, written as an unqualified statement on death certificates, ranks eighth in the leading causes of death at all ages. In most hospitals more time and money are spent taking care of a small group of premature infants than on all the much more numerous larger infants.

Nursery care has improved sufficiently in the last few years to have been responsible for a considerable decrease in mortality rates of infants born prematurely. It is apparent, however, that the frequency with which infants are delivered prematurely must be decreased if there is to be any appreciable gain in infant salvage. To prevent prematurity is the problem.

PREMATURITY: DEFINITION AND INCIDENCE

A premature infant has been accepted as one who weighs 2500 gm. or less at birth. This figure was arrived at from clinical observation of the fact that, in general, infants weighing more than this amount were thought to do better and to be less likely to die than those under this weight. Actually, the median weight of white babies born in most sections of the United States is slightly over 3400 gm., or 900 gm. in excess of the minimum "mature weight." The average length of gestation for an infant weighing 2500 gm. is in the vicinity of thirty-four weeks.

The lower limit of weight or length of gestation that should be used in calculation of incidence of prematurity as separate from abortion, or in establishing premature mortality rates, has not been well established. According to law all liveborn products of gestation are required to be

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registered as live births, but in many institutions an infant so small that it is known not to be viable is considered an abortion even though born alive. It is consequently often impossible to make direct comparisons between one institution and another.

The term "previable" has been recommended for the liveborn infant weighing less than 1000 gm. This has met with some objection on the grounds that occasionally infants below this weight survive and that as methods of care improve, infants of lower and lower weight groups may be expected to live. It is true that in the last few years there has been a slight increase in survival rates of infants weighing in the vicinity of 1000 gm. at birth, but it is a vain hope to anticipate any appreciable lowering of the weight below which infants can survive outside the uterus. It is at approximately 1000 gm. that the lungs and other organs become sufficiently mature to do for the infant what the mother's body does previously. The inadequate vascularization of the lung is the immediate cause of death of almost all liveborn infants under 1000 gm., and pulmonary disturbances continue to be a leading cause of death in heavier premature infants.

Whether one accepts as premature an infant weighing from 1000 to 2500 gm. at birth, or any product of conception born alive weighing 2500 gm. or less, the delineation of the group is entirely arbitrary. The termination of pregnancy, like any physiologic process, cannot be expected to occur invariably at any one point; when the number of infants is plotted against weight at delivery, a symmetric curve is produced. We have made such a curve for 23,868 infants delivered from July 1, 1946, to July 1, 1952, at the Chicago Lying-in Hospital. It shows the greatest number, 5173, of infants weighing from 3251 to 3500 gm. The number weighing from 1001 to 2500 gm. (1455) is not much different from the number weighing over 4000 gm. (1844). If the intermediate group is expanded to a range from 2250 to 4250 gm., the number of infants weighing less than this and the number weighing more are very similar (847 and 739 respectively), 94 per cent of the births taking place when infants weigh from 2250 to 4250 gm. When the mortality rates are investigated, it is found that in infants weighing over 1000 gm. there is no point at which there is a sharp change when the units under consideration are sufficiently small. Total perinatal mortality (fetal deaths and neonatal deaths under ten days) is less than 1 per cent for each of the groups from 3001 to 4500 gm. The lowest rate of 0.4 per cent is the interval at which most births occur—3250 to 3500 gm.

We can thus establish the fact that the time when the greatest number of births occur, in relation to the weight of the fetus, is the most auspicious for the fate of the infant, and that the greater the deviation, especially in the direction of early delivery, the more harmful to the infant.

As in any biologic character, there will always be some variation. Whether or not this variation can be modified is the question.

The incidence of premature delivery as measured by weight varies to some extent in different communities. At the Chicago Lying-in Hospital the frequency has remained remarkably constant and for almost every year since the present hospital opened in 1931 has been between 6 and 7 per cent. Swanson, Lennarson and Adair in 1936 reported that among the first 10,660 live births in the present building, 655, or 6.5 per cent, weighed from 400 to 2500 gm. (Table 1). In a five year study of births

TABLE 1. *Live Births and Neonatal Mortality, Chicago Lying-in Hospital*

	1931–1934			1947–1952		
WEIGHT	NUMBER	MORTALITY PER CENT	FREQUENCY PER CENT	NUMBER	MORTALITY PER CENT	FREQUENCY PER CENT
400–1000 gm.	31	100.0	4.7	60	98.0	4.7
1001–1500 gm.	51	70.6	7.8	127	50.0	10.0
1501–2000 gm.	155	23.8	23.7	220	16.3	17.4
2001–2500 gm.	418	5.9	63.8	858	2.5	68.0
Total	655	19.7 (15.7 over 1000 gm.)	100.0	1265	14.9 (10.9 over 1000 gm.)	100.0
Total live births	10,660			19,351		
Per cent 400–2500 gm.	6.5			6.5		

from July 1, 1947, to July 1, 1952, 6.5 per cent of live births were infants in the same weight group. In spite of the increasing attention given to general prenatal care, weight control, dietary regimens, and so on, the proportionate number of prematures has not decreased at all. The condition of the premature infants, however, has greatly improved, and the mortality for infants weighing from 1001 to 2500 gm. in the first period was 15.7 per cent and only 10.9 per cent in the last period.

FACTORS INFLUENCING PREMATURITY

In order to see whether we might find any conditions that were commonly encountered among women giving birth to premature infants in our hospital, an analysis has been made of the premature births taking place at the Chicago Lying-in Hospital from July 1, 1947, to July 1, 1952. During this period there were 19,791 deliveries of infants and fetuses weighing over 400 gm. Of these, 143 weighed from 400 to 1000 gm., 1300 from 1001 to 2500 gm.* and 18,348 over 2500 gm. They were designated

* In this group 1237 were white, thirty-seven were Negro, twenty were other, and six were unstated. Because of the small number, the nonwhites have not been treated separately.

as previable, premature and mature groups and made up 0.7 per cent, 6.6 per cent and 92.7 per cent of the total births. The fetuses dead at birth included in these figures were 260. Of these, eighty-three weighed 1000 gm. or less, ninety-five from 1001 to 2500 gm. and eighty-two over 2500 gm.

Among 19,531 liveborn infants 260 failed to survive. These included fifty-nine of the sixty weighing 1000 gm. or less, 121 of the 1205 weighing 1001 to 2500 gm. and eighty of the 18,266 weighing over 2500 gm.

Infants and fetuses weighing from 1001 to 2500 gm. made up 6.2 per cent of the total live births.

In examining premature infants in relation to factors pertaining to birth it immediately becomes evident that several groups can be distinguished.

Twins

Those who are twins present a special problem and should be separated from the others because the undue increase in uterine size occasioned by the presence of two fetuses is in itself a condition directly contributing to premature delivery. Included in the present study are 177 twins. (See Table 2.) These are from 108 pregnancies: in thirty-eight cases the birth weight of one twin exceeded 2500 gm.; in one case it was less than 1000 gm. Of the premature twins four died before the onset of labor, one during labor and eleven after birth. This is a total mortality of 9 per cent for the entire group and 6.8 per cent neonatal mortality for those born alive.

Fatal Abnormalities

Severe malformations and erythroblastosis may predispose to premature delivery. Among the single infants there were forty-eight who succumbed from one of these conditions, thirty-five from malformations (twenty-two after birth and thirteen before or during birth) and thirteen from erythroblastosis (three after birth and ten before birth).

Artificial Termination of Pregnancy

Among the women who gave birth to single infants without fatal malformations or erythroblastosis, pregnancy was terminated artificially in 143: by cesarean section in 122 and by induction followed by delivery through the vagina in twenty-one. Sixty-one of the patients whose pregnancy was terminated were toxic, and this was generally the principal indication (forty-six delivered by cesarean section, fifteen through the vagina). The indications for the 122 cesarean sections were previous sec-

TABLE 2. *Complications Associated with Premature Termination of Pregnancy, Chicago Lying-in Hospital, July 1, 1947, to July 1, 1952*

	TOTAL INFANTS	SURVIVING	INTRAPARTUM STILLBIRTHS	ANTEPARTUM STILLBIRTHS	NEONATAL DEATHS	TOTAL MORTALITY	PER CENT MORTALITY
Twins	177	161	1	4	11	16	9.0
Fatal malformations and erythroblastosis	48	—	6	17	25	48	100.0
Labor, induced, toxic	61	49	2	5	5	12	20.0
Labor, induced, nontoxic	82	66	1	3	12	16	20.0
Toxic, not induced	95	79	2	8	6	16	16.7
Antepartum deaths (excluding above conditions)	28	—	—	28	—	28	100.0
Total	491	355	12	65	59	136	27.4
Primary prematurity	809	729	18	—	62	80	9.8
Total premature infants	1300	1084	30	65	121	216	16.8

tion, thirty-six; uncomplicated toxemia, thirty-seven; placenta previa, twenty-seven; abruptio placentae, thirteen; miscellaneous, nine.

Mortality among infants delivered by cesarean section included sixteen neonatal deaths and five antepartum stillbirths. This is a total mortality of 17.1 per cent, or 13.6 per cent neonatal mortality for infants alive at birth. Among the twenty-one patients induced and delivered from below the total mortality was 33 per cent. It included one neonatal death, three intrapartum deaths and three antepartum deaths.

Toxemia

Among women in whom none of the preceding conditions were present—twins, artificial termination of pregnancy, fatal malformations or erythroblastosis—an additional ninety-five were toxic. It is not known definitely whether or not this may contribute to the early termination of pregnancy, but if one is attempting to select a group of women in whom prematurity occurs in the absence of known complications, pregnancies with this complication must be eliminated.

Antepartum Fetal Death

One last group in which premature delivery is a secondary phenomenon is the one in which the fetus dies in utero and is delivered prematurely because of this fact. There were twenty-eight such fetuses dead before the onset of labor in nontoxic women with none of the foregoing conditions.

PRIMARY PREMATURITY

If, from the 1300 premature infants, are deleted those with known conditions which definitely or probably contributed to the prematurity, a group is left in which the premature onset of labor is a primary condition. The groups eliminated include 177 twins, forty-eight with fatal malformations or erythroblastosis, 143 in which pregnancy was artificially terminated, ninety-five with toxemia who were delivered by the vaginal route and twenty-eight antepartum deaths (these are mutually exclusive in the order listed). This is a total of 491, or 37.6 per cent of the original 1300. It leaves 809 infants delivered prematurely, although, as far as could be determined, pregnancy was progressing normally when labor began.

This group makes up 4 per cent of all births, and it is in this 4 per cent that we are especially interested. Why should a healthy woman with a healthy infant go into labor early? Is it part of a biologic variation found in all naturally occurring phenomena, or is it subject to reduction? Why do these premature infants die during labor or after birth?

SURVIVING INFANTS

Among the 809 infants alive at the onset of labor, eighteen died during labor and sixty-two died after birth. This leaves 729, or 90 per cent, who survived. Maternal age in this group shows the same general distribution as for total births at the Chicago Lying-in Hospital, with a peak of 262 between twenty-five and thirty years; 255 were younger, 201 were older, and eleven were unrecorded. There were proportionately more multigravidas than in our total hospital deliveries, with only 287, or 38 per cent, primigravidas. Among the 442 multigravidas, ninety-seven had had one previous abortion, twenty-nine had had two, eleven had had three, five had had four, and one had had five, a total of 143 women who had had one or more abortions. Among all patients 19 per cent had had earlier abortions; among multigravidas 32 per cent had had earlier abortions. This is a considerably higher rate than among patients delivered of mature infants.

Forty-four women had lost children previously by stillbirth or neonatal deaths. Sixty-three of the multigravidas had no living children. There was, however, a total of 607 living children among the remaining 379 multigravidas. Among all the 442 multigravidas there were 874 pregnancies; of these, 607 ended successfully. This is an average of 1.3 living children and 0.6 unsuccessful pregnancy. Thirty-one per cent of all previous pregnancies in multigravidas ended unsuccessfully.

Among the 442 multigravidas the pregnancy immediately preceding the birth of the premature baby terminated in the birth of a surviving mature infant in 262 cases, and a surviving premature in fifty-seven instances; in only seventy-two per cent was the immediately preceding pregnancy successful in producing a normal living infant. The remainder terminated in ninety-one abortions, twenty-one stillbirths or neonatal deaths (seventeen previable or premature infants, three term and one of unknown weight), two surviving but malformed infants and nine in whom the outcome was unrecorded.

The time elapsing between the birth of the present child and the end of the last pregnancy was less than one year in fifty-six instances, from thirteen through thirty-six months in 231, thirty-seven through sixty months in ninety-seven and over five years in forty-two, with the remainder unrecorded. Among the primigravidas in whom there was a record of time interval between marriage and delivery there were 127 married less than two years, fifty-three from two to five years and thirty-five over five years. Only seven were unmarried.

In seventy-five, or approximately 10 per cent, there was a history of threatened abortion.

The first sign of impending labor was pain in 357, rupture of membranes in 249, bleeding in fifty-three, and a combination of factors in fifty-five, with fifteen unrecorded.

Complications existing during labor that were not severe enough to have caused fetal or neonatal death were placenta previa or low-lying placenta, eleven; some degree of abruptio placentae, nineteen; and cord prolapse, four.

The weights of the infants in this group were predominantly in the upper brackets of prematurity with over half (410) weighing from 2251 to 2500 gm. and 176 weighing from 2000 to 2250 gm. In the four 250-gm. intervals between 1001 and 2000 gm. there were fifteen, twenty-four, thirty-seven and sixty-seven respectively. Thus actually only 143 (20 per cent) of this group of 729 surviving infants classed as primary prematures weighed less than 2001 gm., with 80 per cent weighing over 2000 gm.

The sex distribution was 346 (47 per cent) males and 383 (53 per cent) females. This is a reversal of the sex ratios in total births.

NEONATAL DEATHS

Among the premature infants who died after birth, sixty-two of the total 121 fall in the group of primary prematurity.

The mothers of these infants show a normal age distribution with about one third (twenty-one) between twenty-five and thirty with an equal distribution (nineteen each) in the younger and older periods. About one third (twenty-two) had had no previous pregnancies, and ten additional women had no living children. Twelve had had previous abortions, seven had had a previous pregnancy terminate in stillbirth or neonatal death. The thirty women with one or more living children had had a total of forty-two pregnancies. In all there had been seventy-seven previous pregnancies with thirty-two unsuccessful, forty-two successful and two unrecorded. This is an average among multigravidas of one successful pregnancy and 0.8 unsuccessful pregnancy each.

The last preceding pregnancy was successful in twenty-five instances, ending in the births of six premature and nineteen mature infants. There were eight abortions, five stillbirths or neonatal deaths, one surviving but malformed infant and one unrecorded outcome. The time elapsing between the birth of the last infant and the one in this series was less than one year in eight, one to three years in twenty-four, three to five years in seven and over five years in one. Of the primigravidas eight had been married less than two years, seven for three to five years, and two over five years.

In ten (16 per cent) there had been some indication of a threatened abortion. The first sign of impending labor was pains in thirty-four, ruptured membranes in ten, bleeding in seven, and a combination of these in ten, with one unrecorded.

In five there was an associated placenta previa or low-lying placenta, and in five abruptio placentae.

The weight distribution was predominantly in the lower groups in contrast to the surviving infants. Only two were over 2250 gm. and only seven from 2001 to 2250 gm. The distribution in the four intervals between 1000 and 2000 gm. in ascending order is twenty-six, twelve, eight and seven respectively. The neonatal mortality in the primary premature group varies from 32 per cent in those from 1001 to 1250 gm. to 0.5 per cent in those from 2251 to 2500 gm., with an average of 7.8 per cent for this entire group (Table 3). This is in contrast to 10 per cent neonatal

TABLE 3. *Mortality by Weight among Infants without Definite Cause for Prematurity,* Chicago Lying-in Hospital, July 1, 1947 to July 1, 1952*

WEIGHT IN GRAMS	TOTAL INFANTS	SURVIVING	NEONATAL DEATHS	PER CENT DEATHS
2251–2500	412	410	2	0.5
2001–2250	183	176	7	3.8
1751–2000	74	67	7	9.4
1501–1750	45	37	8	17.7
1251–1500	36	24	12	33.3
1001–1250	41	15	26	63.4
1001–2500	791	729	62	7.8

* Infants who were twins, fatally malformed or erythroblastotic, or in cases of artificial termination of pregnancy and/or maternal toxemia have been eliminated from this group.

mortality for the total 1205 liveborn infants delivered during the period under study.

The sex distribution is forty-one males, twenty-one females. For infants born alive in this primary premature group the mortality for males was 10.5 per cent, for females 5.1 per cent.

The length of survival was less than twelve hours in twenty-four, twelve to twenty-four in nine, twenty-four to forty-eight in eighteen, with only eleven dying after forty-eight hours. In most of the writings on premature infants of fifteen and twenty years ago, particularly those concerned with the care of prematures, it was considered logical to exclude from mortality figures all infants who did not survive at least forty-eight hours. If this were done in the present case, the mortality for this primary premature group would be only 1.2 per cent.

INTRAPARTUM DEATHS

The small group of eighteen infants who died in the intrapartum period show much the same maternal factors as those who died neonatally. The sex distribution is more nearly equal, with ten males and eight females. There were five primiparas, with the last preceding pregnancies in the thirteen multigravidas ending in abortion in five instances

and stillbirth once. Half of the women were from twenty-five to thirty years of age with four younger and five older.

CAUSES OF MORTALITY

Among the 791 liveborn infants when pregnancy was not complicated by any of the conditions listed there were sixty-two deaths, a frequency of

TABLE 4. *Causes of Death among Premature Infants Weighing 1001–2500 Gm.,* Chicago Lying-in Hospital, July 1, 1947, to July 1, 1952*

	TOTAL				SELECTED*			
	ANTEPARTUM STILLBIRTHS	INTRAPARTUM STILLBIRTHS	NEONATAL DEATHS	TOTAL	ANTEPARTUM STILLBIRTHS	INTRAPARTUM STILLBIRTHS	NEONATAL DEATHS	TOTAL
No abnormality	40	2	5	47	28	2	4	34
Intracranial hemorrhage	—	2	5	7	—	1	3	4
Anoxia:								
Abruptio placentae	7	10	3	20	—	6	3	9
Placenta previa	—	2	2	4	—	2	1	3
Other	1	7	4	12	—	7	—	7
Malformations	7	7	24	38	—	—	—	—
Erythroblastosis	10	—	3	13	—	—	—	—
Pneumonia	—	—	10	10	—	—	8	8
Hyaline membrane	—	—	52	52	—	—	39	39
Pulmonary, other	—	—	8	8	—	—	—	—
Liver necrosis	—	—	5	5	—	—	4	4
Total	65	30	121	216	28	18	62	108

* Infants who were twins, fatally malformed or erythroblastotic, or in cases of artificial termination of pregnancy and/or maternal toxemia are eliminated.

7.8 per cent. The deaths shown in Table 4 include four due to anoxia from placenta previa and abruptio placentae (first diagnosed during labor), three from intracranial hemorrhage and four from liver necrosis of unknown cause. In four there were no abnormalities demonstrated at autopsy, and all the remaining forty-seven deaths were due to pulmonary disturbances. Eight of these were pneumonia, thirty-nine were a result of hyaline membranes accompanied by secondary atelectasis. This group of deaths associated with hyaline membranes accounts for 63 per cent of the total neonatal mortality in the primary premature group.

Deaths during labor numbered eighteen: fifteen of these were caused by anoxia, six in association with abruptio placentae, two with placenta previa and seven from other or unknown causes; one was caused by intracranial hemorrhage, and in two no abnormality could be found. These deaths are also probably attributable to anoxia.

Even after the deletion of the conditions definitely contributing to prematurity we find twelve deaths (four neonatal deaths and eight intrapartum deaths) resulting from abnormal states of placenta previa or abruptio placentae which were either diagnosed for the first time during labor or were not considered of sufficient significance to warrant induction of labor. Total antepartum and neonatal deaths after the exclusion of these eight total 8.5 per cent and include four intracranial hemorrhage, four liver necrosis, six unknown, seven anoxia of unknown etiology, eight pneumonia and thirty-nine hyaline membrane and secondary atelectasis.

DISCUSSION

The onset of labor, like all biologic processes, has a certain range with a peak at one point and a distribution on each side that produces a symmetric curve. When this is calculated in relation to weight, the maximum number of births is found between 3250 and 3500 gm., with an almost equal distribution on both sides.

In most large studies of premature infants that have been published in the United States the percentage of those weighing 2500 gm. or less has been about 6 per cent for white infants, with figures considerably higher for Negro infants. Whether this is a result of the maximum number of Negro births being in a lower weight category or a result of a wider spread with less of a peak at a given point is not apparent from the available data.

In the study at the Chicago Lying-in Hospital extending from July 1, 1947, to July 1, 1952, there were 1300 infants delivered who weighed from 1001 to 2500 gm. In 38 per cent some known abnormality was associated with the premature onset of labor. This included twins, 13.6 per cent; artificial termination of pregnancy, 11 per cent; fatal malformations or erythroblastosis, 3.7 per cent; maternal toxemia, 7.3 per cent; and antepartum deaths exclusive of those which were included in the foregoing categories, 2.2 per cent. In an additional 1 per cent placenta previa or abruptio placentae caused intrapartum or neonatal death by producing fetal anoxia. In 61 per cent no abnormalities were recognized, and an apparently healthy woman carrying a fetus free of malformations or erythroblastosis went into labor spontaneously before the fetus had attained a weight of 2501 gm.

The first sign of labor in the women without known complications was pain, 30 per cent; ruptured membranes, 20 per cent; bleeding or bloody show, 5 per cent; and a combination of factors in 5 per cent.

Women whose infants died and those whose infants survived showed

no appreciable differences in age from our general hospital population. There were proportionately more multigravidas in both groups than in the hospital population, and a higher proportion of previous pregnancies was unsuccessful. The ratio of previous successful to unsuccessful pregnancies was slightly lower in women whose infants died in the neonatal period, 1:0.8, than in those whose infants survived, 1.3:0.6, 44 per cent having ended unsuccessfully in the first group and 31 per cent in the second group.

The sex distribution was different in the two groups with 47 per cent of the surviving infants being males, while those dying in the neonatal period were 66 per cent males. The mortality for the males (10.5 per cent) was twice as great as for the females (5.1 per cent).

The mortality rates for infants weighing from 1001 to 2001 gm. show a marked increase over those weighing more than 2000 gm., and are more than fifty times the rate for infants from 2250 to 2500 gm. Infants weighing from 2001 to 2500 gm. make up 80 per cent of the infants in the primary premature group.

The principal cause of neonatal death in the group of infants from 1001 to 2500 gm. is abnormal pulmonary function, 63 per cent being a result of hyaline-like membranes with secondary atelectasis.

CONCLUSIONS

From this study it is evident that about 40 per cent of premature births are associated with definite causative factors intrinsic to that pregnancy. In the remaining 60 per cent labor follows premature rupture of membranes or bleeding in half (30 per cent), and in half (30 per cent) painful uterine contractions are the first indication of labor.

There is a higher percentage of multigravidas in this 60 per cent of patients than in the general hospital population, and they have had proportionately more pregnancies ending unsuccessfully than have our total multigravidas. This would indicate that some fundamental disturbance which operates through more than one pregnancy may be of importance as a causative factor in primary prematurity.

Eighty per cent of all the infants in this primary prematurity group weighed over 2001 gm.: the neonatal mortality is only 1.1 per cent; for the 20 per cent from 1001 to 2000 gm. it is 26 per cent. It is this last group that really constitutes the premature problem. In this series there were 196 infants born with a weight from 1001 to 2000 gm.; this is 1 per cent of the total births. Fifty-three of these infants died; this is 26 per cent of the total neonatal mortality among 19,471 infants born alive with a birth weight in excess of 1000 gm.

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RESUSCITATION OF THE NEWBORN PREMATURE INFANT

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Failure to establish postnatal respiration is the cause of more than half of the deaths of prematurely born infants in the early neonatal period. In addition, there is little doubt that many of the babies who survive, suffer varying degrees of permanent cerebral damage from the anoxia associated with delay in establishing effective respiration. It is obvious that any considerable reduction in the neonatal mortality of premature infants will depend upon the development of improved methods of dealing with this problem.

A great deal has been accomplished in preventing some of the other causes of early death. Infection can largely be controlled. Improved obstetric technique has lessened the danger of birth injury. Even the blood dyscrasias can be partially managed. Some day the cause of congenital anomalies may be known, and they may be prevented. However, if all these conditions were brought under control, the main cause of death in these patients would still remain. This is made clear in the exhaustive study by the Chicago Board of Health[1] of the causes of death in 8905 infants upon whom careful autopsies were performed. Dr. Edith Potter, who performed most of these autopsies, has introduced the term "abnormal pulmonary ventilation" to cover the group of infants in whom no other satisfactory cause of death could be found. Table 5, copied from her report, shows the causes of death in infants of varying birth weights. It bears out most conclusively, not only the effect of the degree of maturity upon survival, but also that failure to establish respiration increases in importance as weight decreases. In all groups, however, it is the dominant cause of death. This is the area in which the least progress has been made and to which we must direct our attention before the early neonatal mortality rate will be appreciably lowered.

There are two general ways in which this must be approached: (1) through obstetric research into the causes of premature birth and of

TABLE 5. *Number and Percentage Distribution of Neonatal Deaths by Weight at Birth, by Cause of Death, in Chicago, 1936–1949*

CAUSE OF DEATH	WEIGHT AT BIRTH						
	Total	Under 1000 Gm.	1000–1749 Gm.	1750–2249 Gm.	2250–2500 Gm.	Over 2500 Gm.	Unknown
All deaths	8905	1648	2087	1079	543	3000	548
Abnormal pulmonary ventilation	3890	1201	1185	418	156	659	271
Injuries at birth	1482	204	342	170	83	610	73
Malformations	1404	59	169	197	136	765	78
Infections	1197	111	226	168	97	519	76
Blood dyscrasias	472	19	60	60	43	271	19
Anoxia	337	52	98	57	19	91	20
Miscellaneous	123	2	7	9	9	85	11
	Percentage Distribution						
All deaths	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Abnormal pulmonary ventilation	43.7	72.8	56.8	38.6	28.7	22.1	49.5
Injuries at birth	16.6	12.4	16.4	15.8	15.3	20.3	13.3
Malformations	15.8	3.6	8.1	18.3	25.0	25.5	14.2
Infections	13.4	6.7	10.8	15.6	17.9	17.3	13.9
Blood dyscrasias	5.3	1.2	2.9	5.6	7.9	9.0	3.5
Anoxia	3.8	3.2	4.7	5.3	3.5	3.0	3.6
Miscellaneous	1.4	0.1	0.3	0.8	1.7	2.8	2.0

intrauterine asphyxia with a view to prevention; and (2) improved methods of establishing respiration in the apneic or asphyxiated baby. The latter depends upon better understanding of the physiology of the respiratory mechanism and the development of physiologic methods of correcting abnormal conditions.

IMPORTANCE OF DEGREE OF MATURATION OF THE FETAL LUNG

Unless the pulmonary tissue of a prematurely born infant is sufficiently developed to perform the function of gaseous exchange, it is obvious that no method of expanding the lungs or of providing oxygen will be of any avail.

The lung, unlike most other vital organs, has no apparent function during intrauterine life, but must complete its development and be prepared to function as soon as the baby is born. Until about the fifth month there is no alveolar tissue, and the rudimentary bronchioles are lined only with cuboidal epithelium which is not capable of absorbing oxygen. Soon after the fifth month, alveoli which are lined with respiratory epithelium begin to develop, but it is not until nearly the seventh month that there are enough of them to sustain life. The more mature the fetus, the more functioning alveoli are present. Another characteristic of the immature lung is a deficiency of elastic tissue. This interferes with proper expansion and predisposes to easy collapse. Maturity bears a close relationship to birth weight, but is by no means determined by it, which accounts for the occasional survival of babies of very low weight, while considerably larger ones may not be able to sustain life. This lack of pulmonary development is the primary reason why few babies of less than seven months' gestation are capable of extrauterine existence no matter how generously oxygen may be supplied. Naturally, the more underdeveloped the pulmonary system, the more susceptible is it to other factors which may interfere with its function, particularly to adequate expansion, obstruction by foreign material, and the various things which may cause asphyxia. This makes it clear why deaths from "abnormal pulmonary ventilation" increase in direct proportion to the immaturity of the fetus.

PHYSIOLOGY OF THE ESTABLISHMENT OF RESPIRATION

During intrauterine life, respiration in the sense of gaseous exchange takes place through the placental circulation. The lungs are passive and do not function during fetal life. Their development must be completed, however, and they must be prepared to assume the full function of respiration upon the birth of the fetus. As far as the lungs are concerned, their ability to do this depends upon two things: first, the degree of

maturity of development they have attained, and, second, the effectiveness of the mechanism of breathing in accomplishing adequate ventilation. Probably after the seventh month the lungs are usually well enough developed to carry on respiration, provided breathing can be established. What we really are concerned with is not so much the establishment of respiration as the establishment of breathing.

It stands to reason that so important a function as breathing is something that does not start abruptly at birth. The mechanism of breathing is operative long before the fetus is viable. There is probably little difference between antenatal and postnatal breathing except that, of course, amniotic fluid instead of air enters the lungs in the former and that actual expansion of the thorax and of the lungs is minimal. Therefore postnatal breathing is merely the continuation of an already established function. There is ample evidence to support this statement. Animal experiments and human observations indicate that respiratory or breathing movements take place from about the fifth month, or about the time when the mother first feels "life." At first these movements are spasmodic and irregular, but increase in vigor as the fetus grows. There has been a great deal of argument as to whether or not in the later stages of intrauterine life respiratory movements occur in regular rhythm or are initiated only in response to certain stimuli, i.e., anoxia, increased carbon dioxide tension or mechanical irritation. This is largely an academic question, because during every delivery (except perhaps cesarean section) all these stimuli are present. At any rate there can be no doubt that the normal infant has been making respiratory movements before he is born and that just as soon as the head is delivered (within two to five seconds) he makes his first extrauterine effort.

It is remarkable that so little consideration has been given to the physiology of labor from the viewpoint of the baby. Whole libraries have been written about it from the viewpoint of the mother. The baby is usually regarded as a passive actor in this enormously important process except for the traumatic injuries which may be inflicted upon him. That normal labor during a normal delivery of a normal child has important functions in preparing the baby for extrauterine life has received scant attention.

During labor the amniotic sac ruptures and the amniotic fluid drains away slowly, usually over a period of several hours. Not only does the free fluid drain away, but the excess fluid in his lungs, gastrointestinal tract and body tissues is gradually squeezed out of him by the powerful uterine contractions. This prepares him for the transition from an aquatic to a dry-land existence. It also helps to explain in part why the baby does not drown in the amniotic fluid and further lends possible explanation of the frequent occurrence of "hyaline membrane disease" in babies born by

cesarean section and in premature infants when labor may have been short or its full effectiveness has not been operative. Under these circumstances excessive amounts of amniotic fluid remain in the lungs. Furthermore, the uterine contractions undoubtedly stimulate and arouse the baby to a high degree of muscular activity. Normal infants are not born asleep, but are "fighting mad" from the treatment they have been getting. It is not reasonable to assume that a baby that makes such vigorous respiratory attempts one minute after birth was not making similar efforts one minute before birth.

In the premature infant other important factors are present which interfere with the establishment of pulmonary ventilation. The more premature the infant, the more pronounced are these factors. These are immaturity of the respiratory center, weakness of the musculature of the thorax and diaphragm, easy collapse of the larynx and trachea, and increased resistance to expansion of the underdeveloped lung. Expansion of the lung of the newborn infant may be accomplished in one of two ways: by negative pressure on the pleural surface resulting from expansion of the thorax, which is of course the normal manner, or by positive pressure of air through the trachea, which is artificial. Experiments by Wilson and Farber[3] have demonstrated that in the full term infant at least 25 cm. of water pressure on the trachea are necessary to expand the lung. How much more or less may be required in the premature infant has not been determined, but it is probably more. The full term infant is able to produce much more than this amount of negative pressure by the muscular expansion of the thorax, so that failure to breathe immediately upon birth can occur only in the case of some highly abnormal condition, i.e., obstruction to the airway, damage to the respiratory center, excessive anesthesia or analgesia, or severe anoxia. In the premature infant, on the other hand, none of these extraneous factors may be present, and yet he may not be able to establish breathing because the musculature of the thorax and diaphragm is not strong enough to expand the thorax. It has been further demonstrated that pressures of 40 cm. of water or more, if maintained for even short periods, may, instead of expanding the thorax, cause rupture of alveoli or small bronchioles. This in turn leads to escape of air into the interstitial spaces and the production of emphysema. Once this has happened, it tends to increase steadily, and is usually quickly fatal. This is a common accident in small prematures, in whom 40 cm. of pressure are not sufficient to expand the thorax, but are sufficient to cause a break in the integrity of the pulmonary tree. Consequently, any effective method of establishing pulmonary ventilation will depend upon the development of sound physiologic methods of helping the infant to expand his lungs without damaging them.

CAUSES OF ASPHYXIA

Asphyxia is defined as any reduction below normal of the amount of available oxygen in the circulating blood. There are many ways in which it may be produced in the fetus or newly born infant:

A. Before birth
   1. Interference with the placental circulation
      a. Placenta previa
      b. Abruptio placentae
      c. Compression of the umbilical cord
   2. Severe anemia of the mother
   3. Low blood pressure of the mother
   4. Excessive maternal sedation or anesthesia

B. After birth
   1. Obstruction of the airway
   2. Congenital defects
      a. Cardiac defects
      b. Diaphragmatic hernia
      c. Lung cysts
      d. Tracheo-esophageal fistula
   3. Dysfunction of the respiratory center
      a. Shock
      b. Cerebral hemorrhage or other trauma
      c. Excessive sedation and anesthesia
      d. Anoxia
   4. Immaturity of the respiratory mechanism.

Almost all these causes of asphyxia, except immaturity of the fetus, are problems for the obstetrician. They need not be dwelt upon here. Many of them are preventable, so that a high degree of obstetric skill and foresight is an important factor in reducing early neonatal mortality in premature infants. It is of course apparent that if, in addition to a considerable degree of prematurity, the infant is further handicapped by one or more of the other factors which may cause asphyxia, his chances of survival are proportionately lessened.

Prevention of asphyxia should be a main consideration in reducing premature infant mortality. As just stated, this is an obligation of the obstetrician. First of all, every known means compatible with the welfare of the mother should be used to prolong the pregnancy as much as possible in order to permit the fetus to attain maximum maturity. Secondly, all proceedings during labor and delivery which are known to contribute to asphyxia should be avoided.

In the case of placenta previa or abruptio placentae every effort should be made to deliver the infant as expeditiously as possible. This is usually best accomplished by emergency cesarean section. Unfortunately, this is a complication that can seldom be foretold and one which presents a tremendous hazard to the baby. Not only is his supply of oxygen interfered with, but he may also lose considerable blood through breaks in the placenta. These accidents result in a high degree of immediate mortality, and a large number of the infants who survive, suffer permanent cerebral

damage from the severe and prolonged cerebral anoxia. It is hoped that some day obstetric methods of predicting these accidents may be developed.

It has been amply shown beyond any doubt that sedatives and general anesthetics cannot be given to the mother without affecting the baby. Furthermore, the infant's margin of tolerance for these drugs is much less than his mother's, so that what might be entirely physiologic and safe for her may be highly toxic or even fatal to him. In the case of the premature infant this is even more true. It therefore becomes axiomatic that all maternal sedatives should be kept to an absolute minimum and that general anesthesia should rarely if ever be used, certainly not beyond the first stage of anesthesia. Morphine and allied drugs are particularly hazardous to the infant because of their special action as respiratory depressants and are strongly contraindicated.

RESUSCITATION OF THE ASPHYXIATED OR APNEIC PREMATURE INFANT

When a baby is born that is not breathing or in whom the breathing is inadequate, immediate action is necessary if his life is to be saved or if he is to be spared damage to his brain from anoxia. Only a few minutes of inadequate oxygen supply to the brain are needed to cause irreversible injury. The measures taken to establish respiration must be based on a sound understanding of the physiologic principles involved and a clear knowledge of what has occurred during labor and delivery that may have a bearing on the particular situation.

In large hospitals, particularly those with a full resident staff, a resuscitation team should be organized to bring into play every available skill. This team should include the obstetrician, a pediatrician, the anesthetist and, of course, the nursing staff. Unfortunately there are only a relatively few hospitals in which such a team can be organized. More often than not the obstetrician will be the only one available, and he has the double duty of caring for both mother and child. Whenever a premature birth is anticipated, the obstetrician should try to arrange for assistance to be on hand at the delivery, but many times such deliveries occur at unexpected and inconvenient times.

Furthermore, every hospital, no matter how small or isolated, that pretends to deliver babies should have available for immediate use in the delivery room the best possible equipment for resuscitation. The absolute minimum of equipment consists of oxygen and some apparatus for its administration, some device for aspirating the baby's pharynx, and a means for keeping the baby warm. No hospital is so poor that it cannot provide these things. Failure to do so constitutes gross negligence.

There are three main principles in resuscitating an infant: (1) minimize shock; (2) provide an open airway; (3) get oxygen into the lungs.

This sounds simple enough, but it is astonishing how often some of these principles are violated.

An apneic baby can be compared to an intoxicated man who has been struck by an automobile and knocked to the pavement. He is in a certain amount of shock, he may have a cerebral injury, he is partially anesthetized, and may well have aspirated vomitus or mucus. The most inexperienced person knows that this man must be moved as little as possible, that he must be kept warm and that his mouth must be kept open and his throat cleared so that he can breathe, before anything else is done. The same principles must be followed with the baby.

Minimization of Shock

First of all, gentleness of handling should be emphasized to avoid aggravating any possible cerebral injury or any existing shock. Mechanical means of stimulating breathing such as spanking, artificial respiration, hot and cold tubbing, pouring ether on the skin, dilating the sphincter, and so forth, are not only useless, but may do immeasurable harm. These are the old-fashioned methods of resuscitation which were in general use before the physiology and pathology of the establishment of respiration were well understood. Unfortunately they are still sometimes used by inexperienced persons. Their use indicates a complete ignorance of the basic physiology and pathology involved. Some babies may have breathed in spite of such treatment, none because of it. Even the most thorough efforts of resuscitation need not and must not involve any violent or even vigorous manipulation.

Of next importance is maintaining the body temperature of the baby within a few degrees of normal. The baby has been living in a water bath at about 100° F. temperature. His delivery into what may seem like a hot delivery room may well constitute a drop of 20 or more degrees in his environmental temperature. If he is left exposed to this temperature for even a short time, he will lose heat from his body rapidly. Too great a loss of body heat will further contribute to shock. There are many ways of providing external heat, the best being a preheated incubator or heated bed. Warm blankets may be sufficient with larger babies, but will not be adequate for any length of time with smaller ones. If it is necessary to remove the baby from the incubator to carry out aspiration or other procedures, an ordinary goose-neck lamp with a large bulb and reflector is an excellent method of providing heat. But whatever method used, it is vital to keep the baby warm.

Provision of An Open Airway

It is obviously futile to try to administer oxygen to a baby whose pharynx or trachea is blocked by blood, mucus or other foreign material.

Not only can the oxygen not enter the lungs, but too vigorous attempts to force it in may well further obstruct the passages.

In the vast majority of cases all that is necessary is simple swabbing and aspiration of the mouth and pharynx combined with postural drainage. This does not mean that the baby must stand on his head (a procedure which could conceivably increase a cerebral hemorrhage). If the infant is placed in the prone position on a flat surface, his mouth is lower than his lungs, although moderate lowering of the head may further facilitate drainage. In all babies born by cesarean section it is probably desirable to aspirate the stomach, because considerable amounts of amniotic fluid may remain there and subsequently be regurgitated and aspirated. This is a simple procedure which can be carried out quickly and without trauma. Aspiration of the trachea by means of a catheter introduced into it may sometimes be necessary, but this is a procedure which is done much too often. In the first place it is probably seldom necessary. The occasions on which a plug of foreign material would be in the trachea proper are few. It could probably not happen in an infant who has not breathed at all. Most of the time the obstruction is further down than can be reached through the trachea, in the bronchi and bronchioles themselves.

If tracheal catheterization is done, it should be attempted only by someone skilled in its technique. It is not a simple thing for the uninitiated to introduce a catheter into a premature infant's trachea, and under the best of circumstances it is attended with a certain amount of trauma. Infant laryngoscopes are a great aid, but require considerable skill in their use. It is probably true that many more babies have been injured by inept attempts at tracheal catheterization than have been benefited by its successful accomplishment. One of the great dangers of even successful tracheal catheterization results from attempting to force air or oxygen into the baby's lungs through the catheter, causing a rupture of some part of the pulmonary system. Dr. Potter reports finding many cases of fatal interstitial emphysema which were produced in this way.

Oxygenation of Lungs

After provision has been made to keep the baby warm and the airway has been opened as well as possible, the most difficult part of the resuscitation begins: getting adequate oxygen into the lungs and establishing breathing so that gaseous exchange is possible. The success of this and the methods used to accomplish it will depend on the maturity of the infant and the degree of dyspnea or apnea that exists. It also depends, of course, on the other factors which may be coexistent and which have been mentioned before as contributing to asphyxia. Few of these can be controlled, however, after the delivery has been accomplished.

In larger prematures who are making respiratory efforts most of the time all that is necessary is to administer oxygen by either face mask or an appropriate incubator. In a short time many of these infants will gradually expand their lungs sufficiently to carry on respiration, and after a few days their lungs will be well enough expanded so that they can dispense with the extra oxygen. The smaller infants and those that are suffering from injury, shock or narcosis will need help. Numerous types of mechanical resuscitators have been devised for this purpose. They depend in general upon some method of providing oxygen under positive pressure with or without some means of producing negative pressure on the thoracic cage. This negative pressure may be accomplished either by actual decompression of a cage surrounding the thorax or by rocking the infant so as to cause alternate raising and lowering of the diaphragm. Though these devices may sometimes be useful with full term infants, none of them has proved to be very satisfactory with premature babies. The continued high mortality rate constitutes sufficient evidence to support this statement. One great objection to them is that it is difficult to adjust any such machine to coincide with the respiratory attempts of the infant. If the movements of the machine do not coincide with the breathing of the baby, they may actually interfere with it. Some machines are so made that their rhythm can be controlled by the operator to coincide with the baby's efforts. This is an improvement, but requires a high degree of skill and coordination.

Again, sustained positive pressure executed through the trachea may not be sufficient to expand the lung without danger of rupture of some portion of the respiratory passage and the subsequent development of interstitial emphysema. As stated earlier, experimental evidence indicates that 40 cm. of water is the maximum pressure that can be tolerated for even short periods by the full term infant without danger. This amount of pressure is not sufficient to expand the thorax of a very small weak infant.

The highly controversial Bloxom Air-Lock is probably only a method of supplying heat and oxygen. It is doubtful whether it has any advantage over a well constructed incubator. The physiologists state that gaseous exchange is not aided by the alternating variations in pressure which this machine uses. It does have the indirect virtue of keeping the baby in a closed chamber where he is protected from the overenthusiastic efforts of unskilled personnel.

Another disadvantage of these mechanical devices is that they are too expensive for many hospitals to afford on the basis of the number of cases which could use them. They also easily get out of adjustment and if not used frequently may well be in some inaccessible storeroom when unexpectedly needed.

Probably the most effective apparatus which is now available, which is

not expensive, and which fulfills physiologic requirements as best we can now meet them is simply a tight-fitting face mask connected to an oxygen tank with a rebreathing bag. This bag should be equipped with an automatic cut-off valve so that the pressure cannot exceed 30 cm. of water. The operator can then, by placing his hand on the bag, make alternating pressure and force oxygen into the baby's lungs. This assures against exerting too much pressure and has the great advantage of permitting the operator to make the pressure coincident with the infant's respiratory efforts. This apparatus is simple, inexpensive, can be used by a relatively inexperienced person, and in a considerable number of cases will be thoroughly adequate.

Recently a new concept of expanding the lungs of very small prematures has been advanced by Richard Day[2] and has been further elaborated by Roy Goddard. The essential principle of the concept is that it may be possible to expand the resistant lung of a very small premature by making frequent short blasts of pressure through a tight face mask which are above the limits of safe tolerance if maintained for any length of time. By making pressures up to 40 cm. or even much higher for only fractions of a second at frequent intervals the lung and thorax are gradually expanded without running the risk of rupturing the lung. Experimental work that has been done so far indicates that this method may prove to be highly successful in infants that were formerly hopeless. Equipment is being devised to carry out this procedure which should not be excessively expensive or difficult to operate. It is entirely possible that the next few years will see wide adaptation of this concept.

Mention should be made of the various drugs which have been advocated as respiratory stimulants and which have been extensively used for this purpose. These include Coramine, Alpha-lobelin and Metrazol. Though some of these drugs may provide a brief stimulus to the respiratory center, this effect is quickly followed by one of depression, so that any value of the stimulus is offset. Furthermore, in most instances the trouble is not with the respiratory center, but in the lungs themselves. No amount of stimulus to the center of respiration will strengthen the muscles of the thorax or expand a collapsed lung. The only possible application of these drugs is in those instances in which the respiratory center has been depressed by drugs or anesthetics; situations such as these should be avoided rather than treated.

It is possible that in selected cases of infants who are completely apneic some advantage might be obtained in initiating breathing, but after respiratory efforts have begun their use is contraindicated. Certainly they should not be used to the neglect of the other methods of resuscitation. There may be times when caffeine can be used advantageously to stimulate a very weak infant. If so, the best results are obtained by small, frequently repeated doses.

In instances in which morphine or one of its derivatives has been given to the mother near enough to the time of delivery so that it still might have an effect on the baby, Nalline, which is an antagonist of these drugs, may be helpful. Morphine should, of course, never be given to the mother if at all avoidable, but if some situation has demanded its use, 2 or 3 mg. of Nalline injected into the umbilical vein immediately after delivery may be of value.

PROPHYLAXIS AGAINST INFECTION

Whenever there is evidence of acute infection in the mother, or when the membranes have been ruptured for more than six hours, or it has been necessary to aspirate the baby's pharynx or stomach, and certainly whenever tracheal catheterization has been carried out, measures should be instituted to protect the baby from any infection which may have occurred as a result. After the baby has been resuscitated and it appears that he is going to survive, penicillin in doses of 50,000 or 100,000 units should be administered for two or three days as a prophylaxis.

PREVENTION OF HYALINE MEMBRANE DISEASE

It is not my purpose to discuss hyaline membrane disease here, but it is a well established fact that many premature infants, particularly those born by cesarean section, are prone to this syndrome. After the infant has been resuscitated satisfactorily and sent to the nursery in apparently good condition, the characteristic grunting respiration and chest retraction of this syndrome set in and frequently progress to a fatal termination. Whatever the cause of this condition may be, there seems to be little doubt that it is associated with too rapid drying out of the pulmonary system and that, if the baby is kept in an atmosphere of supersaturated moisture (mist) for a day or two, the incidence of this complication is appreciably reduced. The addition of various wetting agents to the mist has been advocated, but these will destroy equipment that is not specially designed for their use, and most experience indicates that water alone is apparently equally effective. It is a wise precaution, and a measure that can certainly do no harm, to keep all premature infants in supersaturated atmosphere for at least twenty-four hours after birth.

SUMMARY

1. Abnormal pulmonary ventilation is by far the main cause of neonatal mortality in premature infants.

2. The degree of maturity of the fetal lung is a vital factor in determining the infant's chance of survival.

3. All elements which may contribute to produce asphyxia should be avoided so far as possible.

4. Resuscitation involves three general principles: (1) minimization of shock by (*a*) avoidance of trauma and (*b*) maintenance of body temperature; (2) provision of an open airway; and (3) oxygenation of the lungs.

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ERYTHROBLASTOSIS FETALIS IN THE PREMATURE INFANT

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Management of the premature infant with erythroblastosis fetalis presents one of the most interesting challenges and yet one of the most difficult problems of pediatric practice. Prematurity uncomplicated by erythroblastosis fetalis is the main cause of neonatal death. When this condition is coupled with a disease which, without exchange transfusion, has a mortality rate of 50 or 60 per cent, a serious therapeutic problem exists. The severe cases are about equally divided into two categories. In the first are the babies who are stillborn or who are destined to die in the first day of life unless heroic measures are taken. It is in these cases that initial respiratory distress, profound anemia, cardiac failure, edema, electrolyte imbalance and sometimes hemorrhage may be encountered. In the second category are babies who may appear vigorous at birth, but whose condition, if untreated, deteriorates within the first week. The course of these infants may be complicated by jaundice, pulmonary hemorrhage and kernicterus. Anemia is usually a secondary problem. Although the etiologic factors are not always the same, the hazards enumerated are common to erythroblastosis fetalis and prematurity, and it is for this reason that, when the conditions co-exist, the dangers are accentuated. Ideally, therefore, both disorders should be prevented.

ANTENATAL MEASURES

The prevention of prematurity is ordinarily an obstetric problem, but, because of the possible value of early induction of labor in cases of potential erythroblastosis fetalis, the question also can be of special pediatric concern. This point is so controversial that it is to be discussed later at some length. Attempts to prevent erythroblastosis fetalis have been

fruitless; there is a long list of measures which have failed. So far as I know there are only two drugs which are still under trial in the antenatal management of the disease. One is hapten. It has been under investigation for some time, but its value has not been proved. The other is cortisone. Although there are theoretical reasons why it should be helpful in Rh sensitization, reports of results of its use are conflicting. In evaluating these reports it must be remembered that there are such great variations in erythroblastosis fetalis that any new method of treatment must receive widespread trial before it is judged. At present the successful management of erythroblastosis fetalis revolves about early and adequate exchange transfusion.

TREATMENT OF PREMATURE INFANTS WITH ERYTHROBLASTOSIS FETALIS

The value of exchange transfusion for most erythroblastotic infants has been established beyond doubt. It is now clear that kernicterus occurs far less frequently in cases treated by this method than in cases given simple transfusion. Since this complication of erythroblastosis fetalis results in either death or neurologic abnormalities, it is the main hazard of the disease. Therefore if a small or immature baby is seen shortly after birth, there can be no equivocation about choice of treatment. Exchange transfusion should be given as soon as possible, and in many cases it must be repeated. Case I is illustrative.

Case I. Baby B was the third child of a mother whose second baby had died of kernicterus despite one exchange transfusion. The maternal Rh-antibody titer was 1:2048 in saline and in albumin. The husband was homozygous. The third pregnancy progressed normally until the middle of the thirty-seventh week. The fetal movements then became sluggish. Conditions were favorable for induction of labor, and the infant, a boy, was delivered prematurely. His birth weight was 2700 gm. The red blood cell count was only 2 million, but otherwise he appeared in excellent condition. Exchange transfusion was completed at the infant's age of 1½ hours, and he appeared well until 17 hours after birth. Then such disquieting signs as squint, heel lifting and depression of the Moro reflex were observed. With a second exchange transfusion these signs disappeared, and the child at 1½ years is normal.

This case shows the importance of immediate exchange transfusion, even when a baby appears vigorous at birth, and of repeated exchange transfusion in dealing with threatened kernicterus.

Occasionally, of course, a baby is not discovered to have erythroblastosis fetalis until several hours or even days have passed. If the infant is less than twenty-four hours old, we treat it as though it were newly born. If it is a premature infant between one and five days old, blood pigment levels and clinical signs are watched carefully. Although most full term babies who reach the age of seventy-two hours without development of kernicterus are likely to escape this complication, neurologic signs are reported to appear later in premature infants; therefore small or imma-

ture babies should be followed closely for at least five days. If blood pigment levels are high or are increasing rapidly, or if there is any evidence of central nervous system involvement, exchange transfusion should be elected in the hope of preventing or modifying neurologic sequelae. Babies beyond the age of five days are given simple transfusions for anemia only. Cases II and III illustrate these points.

CASE II. Baby S, who weighed 2150 gm. at birth, was referred to us at the age of 36 hours. His hemoglobin was 18.8 gm. per 100 ml.; the red blood cell count 4.6 million, and the serum bilirubin 9.9 mg. per 100 ml. Pigment curves were followed for 5 days; they remained within the limits previously observed in cases of mild erythroblastosis fetalis. The baby continued alert and active and was discharged without treatment. At one month he refused feedings. The hemoglobin was 7.5 gm. per 100 ml., and the red blood cell count 2.5 million. With simple transfusions of packed red cells (5 ml. per pound) he recovered without further difficulty. At 6 months he appears normal.

CASE III. Baby H was the first child of a mother who had been sensitized by blood transfusions in girlhood. The infant, who reached us at the age of 14 hours, was supposedly full term, but weighed only 1800 gm. She was not very anemic (red blood cell count 4 million), but she appeared in only fair condition, and the blood pigment levels were relatively high. Exchange transfusion was attempted by the umbilical route, but after 80 ml. had been given the ductus venosus apparently went into spasm. Transfusion was completed through the femoral vein. The infant's color improved, and the blood pigment levels remained low. However, she took feedings poorly and vomited frequently. The blood potassium was found to be low, and after this deficiency had been corrected she improved rapidly.

Both these infants were past the optimum age for exchange transfusion, and since the first was only mildly affected, treatment was deferred. The maternal history, the clinical appearance and the blood findings in the second case argued for exchange transfusion.

Exchange Transfusion

Techniques of this method of treatment have been described elsewhere. There are a few general points, however, which should be stressed in the care of premature babies. Crucial time may be gained by having serologic determinations in advance of delivery. Case V shows how the cooperation of the obstetrician and the laboratory can help to ensure prompt and successful treatment. It is essential to have a skilled pediatrician or anesthesiologist to assist the operator. Careful as one may be to record data concerning vital signs, there is no substitute for an experienced observer who can evaluate promptly changes in the infant's condition. This assistant also should be capable of aspirating, intubating and laryngoscoping the baby. In the premature newborn the umbilical route is usually the easiest. The Allen needle may be too large for some babies, and we often use only the naked polyethylene tubing. Gentleness must be used in cannulating the vein. Otherwise one may encounter spasm of the ductus venosus or, in rare cases, actual rupture of the vessel. If spasm

of the ductus venosus occurs, the whole exchange may be accomplished through the femoral vein, as indicated in Case III. The farther from the groin one can cut down on the vessel, the less lymphedema is likely to result. The small infant usually does not tolerate well the removal and injection of more than 10 ml. of blood at one time, and we have found that in any case the procedure goes more smoothly with the smaller volume. The amount of blood to be transfused is a matter which must be left to the discretion of the operator. Mollison[11] has published excellent nomograms for relating the amount exchanged to the amount of donor blood left in the infant's circulation. Generally speaking, an exchange equal to the baby's blood volume (35 or 40 ml. per pound) will replace about 60 per cent of the circulating red blood cells; with exchange of twice the estimated blood volume, about 85 per cent of the circulating red blood cells are replaced. As a rule, premature babies tolerate multiple exchange transfusions better than one large replacement, and with small infants we seldom exchange more than twice the estimated blood volume at one sitting.

After-Care

We routinely use Isolettes (special closed type of incubators) for care of premature babies. Oxygen is introduced if there is evidence of real need; usually it can be discontinued after the first seventy-two hours. High humidity is maintained by means of a vapojet with water. Antibiotics are given prophylactically for the first three days. Feedings are begun cautiously; it is not necessary or desirable to start oral feedings until seventy-two hours have passed. At that time glucose solution may be offered, followed by some such low-fat formula as half-skimmed milk. Even with exchange transfusion, some degree of anemia may develop. This and other disturbances of premature erythroblastotic infants are now to be discussed.

MANAGEMENT OF DISTURBANCES OF PREMATURE ERYTHROBLASTOTIC INFANTS

Anemia

Anemia is a disturbance common to prematurity and erythroblastosis fetalis, but anemia of prematurity begins later and reaches maximum severity later than anemia of erythroblastosis fetalis. The chances of survival of all erythroblastotic babies are roughly proportional to the hemoglobin content of the cord blood. In Mollison's[12] series approximately 20 per cent of the neonatal deaths occurred in infants with profound anemia; in some cases there was evidence of cardiac failure. Even if affected infants have adequate red blood cell counts at birth, they

usually suffer severe anemia if they survive untreated. Immediate exchange transfusion temporarily corrects the condition, but the red blood cells may have to be replenished at intervals by simple transfusion. Infants who have received exchange transfusions rarely require further treatment for anemia after the first month of life, but if multiple simple transfusions are used, anemia may persist for two or three months. Rh-negative blood should be used as long as the direct and indirect Coombs tests are positive. Simple transfusion is potentially dangerous, and it is not necessary to keep the red blood cell count at high levels. One must always remember the possibility of transmitting the virus of serum hepatitis; occasionally, introduction of old or fragile cells may increase the serum bilirubin, and administration of whole blood may precipitate hemorrhage. Therefore, after the immediate exchange transfusion (or transfusions) we usually administer no more blood as long as the erythrocyte level is above 2 or 2.5 million. Neither do we routinely give hemopoietic agents such as liver extract, iron, folic acid and vitamin B_{12}. Cases I, II, IV and VI illustrate management of anemia in premature erythroblastotic babies. This complication, as well as other factors, may contribute to another troublesome disturbance of erythroblastotic infants—respiratory difficulty.

Respiratory Difficulty

The functional inadequacy of the immature lung and the tendency of the premature baby to have so-called hemorrhagic pneumonia are well recognized. Even if the lung has matured sufficiently to support life, there may be little or no reserve capacity. Likewise, the lung of a baby with erythroblastosis fetalis, though perhaps for different reasons, may be structurally inadequate or unable to function properly. In serious cases the organ may be the site of congestion, hemosiderosis and erythropoiesis. Some erythroblastotic infants (as well as premature babies) are resuscitated with difficulty at birth, and atelectasis is a common postmortem finding. Cardiac failure may contribute to the early respiratory distress of the very anemic infant. It should not be forgotten also that alterations in blood chemistries may have a bearing on abnormal respirations. If the baby survives long enough for kernicterus to develop, medullary centers may become involved. Thus respiratory difficulty at times is a serious problem in erythroblastosis fetalis; generally speaking, the more immature the baby, the greater the problem is likely to be.

If facilities for immediate exchange transfusion are available, the obstetrician can aid in preventing cardiorespiratory distress by seeing that obviously anemic infants do not receive the full complement of placental blood. This maneuver may be helpful to babies already in cardiac failure, and it decreases the total amount of abnormal blood pigment which

must be removed later. If respirations are not well established, that is, if they are irregular or jerky, it is not always well to defer treatment in the hope that they will become satisfactory. The baby may be in need of venesection; if care is used, the respirations may improve as exchange transfusion proceeds. The venous pressure is usually high (above 8 cm. of blood) in babies with poor initial respirations, and the transfusionist should attempt gradually to withdraw more blood than he injects, building up the deficit a few milliliters with each syringeful exchanged. The amount of the final deficit must be gauged by serial measurements of the venous pressure and by the baby's general condition. The first exchange transfusion usually must be small in infants with respiratory embarrassment (200 to 350 ml.). In cases seen shortly after birth, our studies show that after small exchange transfusions the blood pigments are likely to have returned to the original levels at the end of six hours. We therefore may elect re-exchange transfusion within that period. A third or even a fourth exchange transfusion may be indicated by the levels of blood pigments and the clinical condition. The successful treatment of a baby with severe respiratory distress is described.

CASE IV. Mrs. C had one normal child. A second baby had died despite exchange transfusion. A third pregnancy progressed to the thirty-eighth week, when, because of the maternal history, labor was induced. At birth the infant weighed 6 pounds, but was grossly edematous and pale. The liver and spleen filled the abdominal cavity, and there was a harsh systolic cardiac murmur. The baby was resuscitated with some difficulty, and respirations were poor. Exchange transfusion was begun 10 minutes after delivery. During the procedure there were 2 episodes of prolonged apnea. After 320 ml. of blood had been removed and 280 ml. introduced, the baby was sent to the nursery. At the age of 5 hours he appeared stronger, but was still having trouble breathing, and no Moro reflex could be elicited. The blood pigments were at their original levels. A second exchange transfusion of 410 ml. out and 380 ml. in was performed. After this transfusion, respirations were easier and the color was pink for the first time. The Moro reflex now could be elicited, and the baby was more active. At 9 hours, however, his clinical status again deteriorated. Respirations were rapid and weak; he seemed exhausted, and his Moro reflex was all but absent. There were multiple confluent petechiae over the face and head, and he was cyanotic even in a rich oxygen atmosphere. The blood pigments again had returned almost to their previous levels. A third exchange of 400 ml. out and 400 ml. in was performed. The baby then improved gradually. At 27 hours the blood pigments, while not so high as previously, were abnormal, and a fourth exchange (330 ml. out and 310 ml. in) was done. At 48 hours the infant's appearance was bizarre. He had gross dependent edema of the scalp and thorax and pitting edema of the lower extremities. The respiratory rate had increased, and he was apathetic. The sucking and Moro reflexes were poor. Chemical examination of the blood disclosed potassium deficiency (2.8 mEq. per liter). With intravenous administration of glucose and potassium solution, the baby improved steadily. Development has been normal, and at 5 months the baby is happy, alert and active.

This was a case of early respiratory distress which probably was caused by anemia and resultant cardiac failure. The condition was aggravated later by potassium deficiency. There is no doubt that early and adequate exchange transfusion was lifesaving. This case was complicated by another abnormality, edema.

Edema

Edema is a common disturbance of premature infants, and the tendency of erythroblastotic newborns to have generalized edema is well known. Potter has called attention to the swollen eyes, open mouth and protruding tongue of erythroblastotic stillborn infants even in the absence of severe generalized edema. Infants with hydrops fetalis are likely to be born prematurely, but, owing to the presence of excess fluid, they may be heavier than normal fetuses of corresponding gestational age. Pleural effusion may occur, and occasionally peritoneal effusion is so great as to cause dystocia. Premature erythroblastotic babies without frank hydrops fetalis may undergo rapid weight loss in the first three to five days of life. They sometimes exhibit signs of cerebral edema which resemble those of kernicterus. Unless it is necessary to remove pleural or peritoneal effusions, edema alone need not cause great concern. It is our experience that if anemia is corrected and the electrolyte balance maintained, the infant will diurese gradually and there will be no detectable residual damage. As Case IV illustrates, infusion of hypertonic colloid or crystalloid solutions is not indicated. Signs of cerebral edema may be disquieting, but are transient; with experience one can learn to distinguish them from those of kernicterus. A case of successful management of fetal hydrops uncomplicated by other serious disturbances is given.

Case V. Mrs. A had had 8 previous pregnancies, but only the first baby had survived. At the third month of her ninth pregnancy the anti-D titer was 1:16 in albumin. Her antibody titer was followed regularly at 4 week intervals in the first 2 trimesters; after that, at intervals of 2 weeks. At 28 weeks the titer had risen to 1:1024 in albumin. Three weeks later it fell abruptly to 1:64. This finding was confirmed, and the obstetrician was warned that this significant fall of the antibody titer might herald a stillbirth or the beginning of polyhydramnios. The patient lived in a rural community some distance away, and when she reported to the obstetrician's office a few days later, she had such a degree of polyhydramnios that it seemed urgently necessary to relieve the abdominal distention. In the attempt to do so, a large, boggy placenta was penetrated. The infant was therefore delivered without delay. He had frank hydrops fetalis, but he survived with only one exchange transfusion and at 2 years has no evidence of sequelae.

Fortunately, this case presented no serious problem, but in every such baby the blood chemistries should be watched.

Electrolyte Imbalance

Any premature baby and any erythroblastotic baby may suffer electrolyte imbalance; therefore this complication is not uncommon in affected premature infants. The possibility should always be kept in mind when a newborn fails to do well after exchange transfusion. Hypocalcemia and acidosis are observed most frequently. The premature erythroblastotic baby has been reported to be especially prone to suffer hyperkalemia, but, as indicated, we sometimes encounter potassium deficiency. Elec-

trolyte imbalance is often harder to detect clinically than it is to control. Calcium deficiency may be prevented by administration of 10 per cent calcium gluconate in the course of exchange transfusion. One or 2 ml. of the solution should be given after each 100 ml. of blood exchanged. If the infant ruminates, yawns or seems restless, more should be given promptly. We have used as much as 30 ml. in a single exchange transfusion. Not infrequently infants will show signs of tetany fifteen to thirty minutes after exchange transfusion is completed, and it is good practice to see that the baby is under close medical observation for at least half an hour after he has been returned to the nursery. Use of fresh blood may prevent hyperkalemia. If the patient fails to thrive after exchange transfusion, other electrolyte deficiencies should be sought and corrected. Case IV is illustrative, as is the following example.

Case VI. Mrs. D had one normal child. A second child had died of kernicterus. The mother also had a history of blood transfusion of unknown Rh type. The third pregnancy was complicated by toxemia and was finally interrupted by cesarean section at approximately 36½ weeks because of maternal hemorrhage. At birth the infant, who weighed 2400 gm., was active, but her red blood cell count was only 1.2 million and the hemoglobin 4.8 gm. per 100 ml. The first exchange transfusion was completed at the infant's age of 2 hours. Because of increasing jaundice, a second exchange was attempted at 31 hours, but the baby went into collapse during the transfusion and was resuscitated only after administration of intracardiac epinephrine. The following day she appeared in very poor condition and, while we were examining her, had a generalized convulsion which was not stopped by administration of calcium gluconate. A third exchange was considered imperative, and during the procedure the baby improved visibly. The following day her respirations became rapid and her color poor. The baby had begun to diurese, and her weight had dropped to 2100 gm. Examination of blood chemistries revealed metabolic acidosis. After correction of the acidosis with sixth-molar sodium lactate solution she improved. She required 2 simple transfusions in the first month of life. At 9 months she has no stigmata of kernicterus.

Hemorrhage

Deficiency of coagulation factors and increased capillary fragility may combine in the premature infant to produce hemorrhage. Even with use of exchange transfusion, hemorrhage is occasionally a troublesome complication of erythroblastosis fetalis and is likely to be serious. The causes of hemorrhage in the erythroblastotic newborn have not been made altogether clear. Heyn[7] and associates found no consistent coagulation disturbance in ten erythroblastotic infants, but they reported that on the first day of life the average blood clotting time was increased and in 60 per cent of the cases the protamine titration was above normal adult levels. We have been impressed occasionally with the extreme vascular fragility of badly affected babies.

The earliest and most striking hemorrhages are in the skin. The presence of petechiae at birth or shortly thereafter may portend hemorrhage elsewhere, but does not mean always that fatal bleeding will occur. In

inadequately treated patients pulmonary hemorrhage is common and often accompanies kernicterus. Usually it is not evident until seventy-two hours or thereabouts; in severe cases, signs may appear earlier, however, and simple transfusion of blood is likely to precipitate it at any time in the first five days of life in susceptible babies. Intracerebral bleeding sometimes occurs, and one should always be on the alert for subdural hematoma. Unless hemorrhage is early and severe, it may be controlled with exchange transfusion. To premature infants we also give vitamin K, 2.5 to 5 mg. every four to six hours until the bleeding tendency disappears. Cases VII and VIII are examples of this complication:

CASE VII. Baby Z was born after a difficult labor to a mother who had received transfusions in girlhood and who had had 4 previous unsuccessful pregnancies. Although he was supposedly at term, he weighed only 4 pounds. He was lethargic and had purpura over the face and upper extremities. Anemia was moderate, and the total serum bilirubin was 6.2 mg. per 100 ml. The baby received exchange transfusions of 400 ml. each at 2 hours and at 30 hours. Supportive treatment included vitamin K. At 36 hours the patient had respiratory difficulty; he died 5 hours later. At necropsy pulmonary hemorrhage and a massive left occipitoparietal subdural hematoma were found.

CASE VIII. Baby F was born to a mother who also had had transfusions in girlhood and who had no normal children. The infant was delivered 3 weeks before term after induction of labor. When she reached us at the age of 45 minutes, the face and body were covered with ecchymotic areas. Rales were present at both lung bases. It seemed doubtful whether she would survive exchange transfusion, but the procedure went well. A second exchange was done at the infant's age of 9 hours and a third at 33 hours. Vitamin K also was given. At 20 hours the rales disappeared, and later the ecchymotic areas slowly faded. At one year the baby seems normal.

In the first case, hemorrhage probably had occurred in a vital area before treatment was instituted. The second case, although severe, benefited from treatment. Hemorrhage, fortunately, is no longer a frequent problem in erythroblastosis fetalis. Jaundice is encountered in almost every case.

Jaundice

Average serum bilirubins of premature infants are higher than those of full term newborns; in fact, the bilirubin values of nonerythroblastotic prematures may reach levels as high as those of erythroblastotic babies. Since kernicterus occurs more frequently in the premature than in the full term erythroblastotic baby, and since it occurs far oftener in deeply jaundiced infants than in the mildly jaundiced, it has been suggested that bilirubin itself is responsible for the complication. Hsia[10] and associates as well as Mollison[11] have called attention to the relationship between hyperbilirubinemia and kernicterus. Crigler and Najjar[6] have crystallized abnormal bilirubin from cases of familial nonhemolytic jaundice with kernicterus, and bilirubin has been extracted after death

from pigmented areas of brains of affected babies. Other workers have questioned the bilirubin theory. Bevis[4] has examined antenatal specimens of amniotic fluid in cases of Rh sensitization. He reports that kernicterus in the fetus is related to the icteric index of the amniotic fluid, but he states that the compound contributing to the yellow color is not bilirubin. He suggests that it may be mesobilifuscin.

We have examined amniotic fluid, ascitic fluid, cerebrospinal fluid and blood plasma of infants with hemolytic disease and have found, in addition to bilirubin, abnormal amounts of heme pigment (with maximum absorption at 408 millimicrons). Prognosis can be related to the quantity of this pigment (or mixture of pigments). High levels of heme pigment may be present at birth or may develop in advance of hyperbilirubinemia. Since control of both pigments may be essential to successful management of erythroblastosis fetalis, and since both usually can be kept at presumably safe levels by exchange transfusion, we have found continuous spectrophotometric absorption curves an invaluable guide to treatment. We try, with early and repeated exchange transfusion, to keep the plasma bilirubin below 20 mg. per 100 ml. and the absolute optical density of the heme pigment below 0.100 (when measuring a 1:50 dilution of plasma in saline solution). Under these conditions, of ninety-seven cases of erythroblastosis fetalis seen before the twelfth hour, the over-all mortality was 8.3 per cent, and no child in the series who survived had neurologic sequelae.

Kernicterus

It now is the consensus that in the premature infant conditions exist which favor development of kernicterus; in fact, the premature baby apparently may suffer this complication even in the absence of maternal isosensitization. This complication is the most dreaded of all the hazards of erythroblastosis fetalis and should be foremost in the minds of those who deliberately risk premature delivery of a potentially affected baby. After delivery the pediatrician and nursing staff must be alert to any sign of neurologic disorder. Dysphagia, poor respirations, lethargy, hyperactivity, deepening jaundice and elevation of temperature should be reported promptly. The physician should observe the baby at frequent intervals, noting changes in the character of the cry, loss of sucking and rooting reflexes, abnormal ocular movements, rigidity, opisthotonos, twitching, and alteration or loss of the Moro reflex. *Isolated observations of this reflex are likely to be misleading; it should be followed closely for at least the first seventy-two hours of life in the same baby.* At present, exchange transfusion is the only known method of preventing or modifying the brain damage which may occur, and the treatment should be given if neurologic signs appear or if blood pigment levels are elevated.

Cases I and VI show the difficulty under optimum conditions of dealing with impending kernicterus in the immature newborn. This brings us to a question which is still controversial—the advisability of early induction of labor in Rh-sensitized women.

Premature Induction of Labor

Some years ago this measure was proposed and immediately became popular. This is understandable in view of parents' pleas to "do something" and the dramatic appeal of "taking the baby early." For some time, therefore, a virtually uncontrolled mass experiment was carried out. In 1946, however, Vaughan[14] suggested that early induction of labor might contribute to the development of kernicterus. In a later paper[15] he and associates presented evidence that kernicterus was directly related to the degree of immaturity of the erythroblastotic infant. Their data are significant and useful. Of the stillbirths in the series, about 70 per cent occurred before the thirty-seventh week of gestation and about 30 per cent after the thirty-seventh week. Of infants delivered before the thirty-eighth week, 23 per cent had kernicterus, but neurologic sequelae were not so frequent in the more mature group. These observers did not doubt that premature delivery had prevented certain stillbirths, but this gain was obviously more than offset by neonatal death or survival with motor and mental disability. Later Vaughan[16] reviewed reproductive histories of a number of women, each of whom had borne a series of erythroblastotic babies. The variability of severity of disease was striking, and one may question whether many of the successes ascribed to early delivery were not instances of this variability.

It remained for Mollison[12] to support these conclusions with results of a carefully planned survey. He and his co-workers carried out controlled trials of treatment of babies in twelve hospitals in Britain over a two year period. From this survey of 477 infants with erythroblastosis fetalis they concluded that the practice of inducing labor three to five weeks before term was associated with a lower proportion of surviving infants than was the practice of allowing delivery to occur spontaneously. In selected groups of the series mortality was about four times as high in premature infants as in mature infants. Of the immature babies about 25 per cent had kernicterus.

These reports, which were in line with our own impressions, have led our group to assume a conservative attitude toward early delivery of the Rh-sensitized woman. We do not routinely hold out the hope that induction of labor will influence the outcome favorably. Moreover, in the best interests of the mother, we point out that pregnancy involving a fetus with severe erythroblastosis fetalis may be complicated by polyhydramnios and by serious antepartum, intrapartum or postpartum hemorrhage.

Therefore, before the pregnancy is interrupted, the possible presence of maternal coagulation defects should be considered. We cannot, however, believe that early delivery never should be permitted. In Mollison's series treatment was decided by a series of random numbers, and the premature babies did not all receive exchange transfusion. Nor was re-exchange transfusion used. The facts that (1) 30 per cent of the stillbirths may occur between the thirty-seventh and fortieth weeks, (2) the danger of kernicterus is not so great in this group as in the more immature babies, and (3) exchange transfusion will prevent kernicterus lead us to believe that if certain criteria are met, early delivery may be justified. Before considering these criteria, it is important to emphasize circumstances under which intervention is contraindicated.

Contraindications. 1. If the pregnancy has not advanced to the thirty-seventh week, the chances of saving the baby are small. Our statistics plus data supplied by the Boston Blood Grouping Laboratory indicate that mortality in this group, even with prompt treatment, may approach 40 per cent. In addition, we have seen the double tragedy of death of mother and child after early intervention in aggravated cases. Therefore, delivery should be done before the thirty-seventh week only if there are urgent obstetric indications, as illustrated in Cases V and VI.

2. If the infant weighs less than 2500 gm., our combined data indicate that the chances of survival are a little less than 70 per cent. Therefore, if the baby is believed to be small, it should be delivered only on obstetric indications, as illustrated in Cases V and VI.

3. If the parents already have normal children, the mother should not be encouraged to participate in what is, in some respects, an experimental procedure.

4. If there is evidence that the husband is heterozygous, there is approximately a 50:50 chance of delivery of a nonerythroblastotic Rh-negative baby. Such an infant should not be jeopardized by early delivery.

5. If the maternal titer is relatively low (under 1:64) and there have been no previous erythroblastotic infants or injections of blood, the chances that the baby will survive are good. Again, such infants should not be jeopardized by early delivery.

6. If facilities are not available for immediate care of the infant, it is foolhardy to undertake cesarean section or induction of labor. This point should be self-evident, yet our experience indicates that there are still physicians who ignore or minimize the importance of prompt and expert pediatric care for all erythroblastotic babies.

Indications. If the family is small, if there is evidence that the husband is homozygous, if the pregnancy has reached the thirty-seventh week, and if obstetric conditions are favorable, early delivery may be justifiable in the following circumstances:

1. If the mother has had either a previous erythroblastotic baby or

injections of Rh-incompatible blood, the chances of intrauterine death in general are increased, and early delivery may prevent stillbirth. Cases I, IV and VIII are illustrative. A word of warning should be issued at this point: if the pregnancy of a woman with a history of previous stillbirth advances to the thirty-seventh week, the baby may be Rh negative, and laboratory reports that the husband is homozygous may be in error. In such cases it is a wise precaution to have the laboratory determinations confirmed before early delivery is considered. Although the disease is variable, early intrauterine death of an Rh-positive fetus is more likely to occur in such cases than is death after the thirty-seventh week.

2. If the pregnancy involves a first-affected baby and the maternal titer is high (in our laboratory 1:64 or over), the chances of late stillbirth are probably great enough to warrant intervention.

3. If conditions are such that a child allowed to be delivered spontaneously might not receive prompt treatment, delivery under controlled conditions may be considered. Ideally, no baby should suffer from want of pediatric care, but this ideal is not always realized. Therefore, we have recommended induction of labor in cases in which the mother otherwise might be delivered under unfavorable conditions.

The case material seen under these restrictions is limited, but thus far the results have been little less than miraculous. The cases cited illustrate that, regardless of conditions of delivery, if treatment is prompt, if blood pigments are controlled by re-exchange transfusion, and if the special disturbances which may be encountered are anticipated, the challenge presented by the premature erythroblastotic infant may be met successfully.

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POSTHEMORRHAGIC SHOCK IN THE NEWBORN PREMATURE

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The pallid, flaccid newborn premature is a challenge to the practicing physician or pediatrician. This problem must be met immediately with all the available diagnostic tools and skill in order to change the prognosis from one of sudden death to that of viability. The purpose of this paper is to make the clinician aware of a somewhat neglected and often overlooked cause of sudden death in the premature newborn.

The literature on placenta previa, abruptio placentae, cesarean section and other causes of occult bleeding from placental or umbilical vessels in the last trimester impresses one with the lack of emphasis on the role of severe anemia due to blood loss as an important factor in the death of some of the newborn prematures, and the absence of specific directions on exactly what is to be done about such an emergency.

The purpose of this paper is to discuss the various causes of severe posthemorrhagic anemia in the newborn premature and to present cases which exemplify the differential diagnosis and treatment of the condition.

PLACENTA PREVIA AND ABRUPTIO PLACENTAE

Though prematurity and asphyxia play a much more frequent part in the death of infants born in cases of placenta previa and abruptio placentae, their treatment does not demand the immediate decisive action that posthemorrhagic shock does. To quote Wiener:[16] "The hazards to

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the mother of hemorrhage caused by abruptio placentae and placenta previa are well known, but while it is generally recognized that such cases are attended with a high fetal mortality rate due to asphyxia, little or no cognizance is ordinarily taken of the fact that infants born alive in such cases or even in apparently normal deliveries may be suffering from a dangerous anemia due to occult hemorrhage from the placental or umbilical vessels." Macafee[10] states that the anatomy of the placenta in placenta previa is an important cause of prepartum and intrapartum death of the fetus, and postpartum death of the newborn due to exsanguination anemia.

A placenta previa is usually a thin placenta which covers a large area of the uterine cavity and is frequently lobulated. Furthermore, the umbilical cord often has a marginal or velamentous insertion which in itself is an added risk. If such a cord is inserted at the lower edge of the placenta in close proximity to the internal os, the first hemorrhage may cause the death of the fetus. Macafee analyzed the cause of death in forty-seven stillbirths and newborn deaths in placenta previa, and found that hemorrhage (exsanguination) was the cause of death in nine, or 20 per cent. Five of the cases had a low insertion of the cord of the Batteldore or marginal type. Three cases had a velamentous insertion of the cord, and one a torn vasa previa.

In the past the emphasis in treatment of placenta previa and abruptio placentae was focused on lowering the maternal mortality; with the advent of maternal welfare departments and maternal death committees, and the easy availability of blood, this mortality has reached an almost irreducible minimum. As a result, interest is now being focused on infant survival as witnessed by the advent of fetal death committees, and much research is being done on the problem of the premature infant. In line with this emphasis on fetal salvage is the importance of looking beyond the immediate expectant treatment of placenta previa, with its marked salvage of the premature infant, and even improved maternal salvage, to the prompt and decisive treatment of certain of the infants born suffering from posthemorrhagic anemia and shock.

The volume of literature on the immediate treatment of infants born suffering from anemia of the newborn or erythroblastosis has focused attention on the necessity and techniques of giving blood to these infants. It has emphasized the necessity of having the equipment ready in every obstetric department for instantaneous use. This has all been for the good. But Wiener[16] has pointed out that infants may be born suffering from posthemorrhagic shock from hemorrhage of abruptio placentae, placenta previa, incision into the placenta at cesarean section and the occult placental bleeding into the maternal circulation, which he has postulated may be regarded as hemolytic anemias of the newborn, and valuable time is wasted getting tests done preparatory to an exchange

transfusion when actually a massive regular transfusion should be given, since severe posthemorrhagic anemia, which is often associated with shock, calls for much more vigorous transfusion therapy than hemolytic anemia. In cases in which the mother is Rh positive or, if Rh negative, has neither Rh agglutinins nor glutinins in her serum, the diagnosis of erythroblastosis can be excluded, as a rule, raising in its place the question of possible posthemorrhagic shock.

CASE I. Here the anatomy of the partial placenta previa was the underlying cause of posthemorrhagic shock in the infant. The precipitating causes were the contrac-

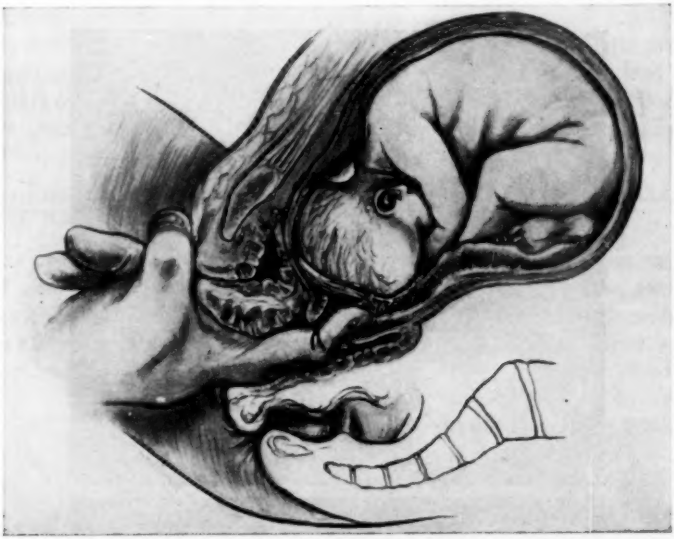

Fig. 1. Intracervical examination in placenta previa may cause fetal placental bleeding: (1) in cases of lower pole insertion of Batteldore or marginal insertion of cord; (2) lower pole attachment of velamentous insertion of cord (therefore vasa previa).

tions of labor and the intracervical vaginal examination (Fig. 1) separating the lip of placenta, which was directly vascularized by a lower pole insertion of a velamentous insertion of the cord (therefore also a vasa previa).

M.G., a 36 year old gravida II, para I, at term, was admitted to Loretto Hospital on August 14, 1949, in active labor. About 3 hours later a considerable amount of bright red bleeding was noted. A sterile vaginal examination revealed an effaced cervix which readily admitted a finger. The circumference of the placenta could be easily palpated overlying the margin of the internal os and on the anterior left lateral surface of the uterus. This examination caused slightly increased bleeding to occur. Membranes were ruptured, and after the flow of the amniotic fluid a trickle of bright red blood was noted. Willetts forceps were applied to the scalp, and traction applied to the handle. Fetal heart tones became slow and irregular. The traction was released, and the patient was placed in reverse Fowler's position and given oxygen and hypertonic glucose solution. The fetal heart tones returned to normal. The patient was taken to the delivery room, where a laparotrachelotomy was done.

The infant was markedly anemic. It appeared white and exsanguinated. It breathed weakly and was flaccid. The liver and spleen were not palpable. The respirations were continued with a tracheal catheter, and 90 ml. of the pint of blood prepared for the mother were started within 15 minutes in the leg vein of the infant, who responded dramatically in color, tone, respiration and cry. Two hours later it again looked pale and weak, and another 70 ml. of blood were given. The infant again responded in a markedly improved manner. Twelve hours later the baby again began to do poorly, and expired 20 hours after birth.

Autopsy revealed a large defect in the interventricular septum of the heart, one of the largest the pathologist had seen. He felt that death was immediately attributable to this condition. The placenta was described by the pathologist as essentially one with a velamentous insertion of the cord, and succenturiate (Figs. 2 and 3).

Fig. 2

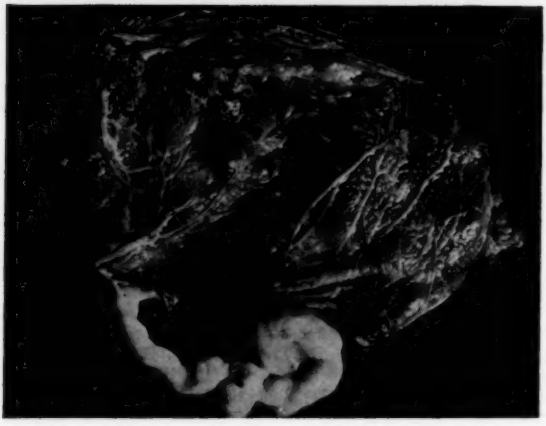

Fig. 3

Figs. 2 and 3. Placenta previa with velamentous insertion of cord into lower edge of placenta and succenturiate lobes at internal os (therefore also a vasa previa).

Here the fetal exsanguination took place through the thin edge of the placenta previa, which was a succenturiate lobe, since it was slightly separate from the remaining body. More important, it was fed by large-caliber umbilical vessels arising from the velamentous insertion of the cord, which began 3 cm. away. This thin piece of placenta previa lying next to the os of the cervix was separated from the uterus during labor and during the examination. Holmes[5] stated: "The placental separation of placenta previa, and tearing, jeopardize the infant by producing intrauterine asphyxia and fetal anemia." He also wrote concerning the causes of death of infants in placenta previa: "Hemorrhage (the third cause of fetal death in placenta previa) may result from placental tearing." Macafee[10] also emphasizes the importance of the architecture of the placenta previa as causing fetal hemorrhage, especially when large blood vessels feed the margin of the placenta near the cervix as in the case of vasa previa, Battledore insertion of the cord, a lobulated placenta or a succenturiate lobe.

INCISION INTO THE PLACENTAL OR UMBILICAL BLOOD VESSELS AT CESAREAN SECTION

Siddal and West[13] reported eleven babies whose placentas were cut at the time of delivery by cesarean section (Fig. 4). Four of these, two of which were premature, had hemoglobins ranging from 9 to 11.5 gm. and red blood cell counts ranging from 2.5 to 3.10 million. These babies were described as pale and listless and were obviously not normal. Two of

Fig. 4. Illustrating potential fetal blood loss factors of cesarean section incision made through large blood vessels of placenta on anterior wall of uterus. (Courtesy of Dr. F. H. Falls.)

them were given blood transfusions of 70 and 50 ml. respectively, with marked improvement resulting. All four were finally discharged from the hospital in satisfactory condition. In addition to the four babies with marked anemia, there were three others, one of which was premature, with hemoglobin levels of 12.2, 12.5 and 12.9 gm. which correspond to percentages of 79, 81 and 84. The accompanying red blood cell counts expressed in millions were 4.12, 4.10 and 3.60. Falls[2] reported a case of anterior insertion of the placenta which was cut in making the cesarean section incision through the region of the insertion of the cord, with resultant fetal shock from hemorrhage. He states that DeLee referred to this type of case as "placenta previa cesarea." When the placenta is encountered at cesarean section, the baby should be delivered, and the cord clamped as quickly as possible to lessen blood loss from cut fetal placental vessels. In cases of placenta previa the transverse low flap operations should probably be abandoned in favor of the vertical incision, which should start superiorly and, if the placenta is cut down on it, should be separated and pushed aside—not incised.

Case II. R.M., a 38 year old gravida II, para 0, whose estimated date of delivery was September 17, 1949, was admitted to Loretto Hospital August 8, 1949, because of vaginal bleeding which began just prior to entrance. Shortly after admission the bleeding stopped. Roentgenograms were taken and revealed the infant in a transverse presentation. The location of the placenta was not definite in the lateral films, but the soft tissue shadow seemed to be situated low in the uterus and even bordering the internal os. The patient was placed at absolute bed rest. It was felt that, since this was a 34 week gestation, carrying the patient along on expectant management would give the infant a better chance to survive. Because of a hemoglobin of 9.9 gm. and a red blood cell count of 3.26 million, the mother was given a blood transfusion. On August 20, 1949, after another episode of bleeding, a low cervical cesarean section was done. The infant, born in a left anterior scapula position, weighed 4 pounds 10 ounces, breathed and cried immediately, but its color was ashen. Examination of the chest revealed pulmonary atelectasis. The red blood cell count was 4.0 million, and the hemoglobin 14.8 gm. The infant expired within 48 hours of birth.

At the time of section the placenta was found attached to the anterior surface of the uterus, and down over the cervical os. It covered the lower third of the incision and exhibited a succenturiate lobe of moderate size with many medium-calibered blood vessels running into it. From a study of the placenta and membranes after delivery it appeared that the succenturiate lobe was in the region of the trachelotomy incision. It is possible that the operator, in separating the upper fourth of the placenta from the uterus in order to get his hand in to grasp the feet of the fetus in the transverse lie in order to do a version and extraction, might well have taken enough time in doing the delivery to allow fetal blood loss to occur from the well vascularized, thin, succenturiate lobe and margin of the placenta.

Despite the fact that the autopsy revealed prematurity, atelectasis and petechial hemorrhages of the brain as the main causes of death of the infant, it seems justified to offer this case as one which also may exhibit blood loss factors. There is a possibility here that anemia was an important contributing factor in the infant's death. Wiener,[16] in a discussion of a case of occult placental bleeding from placenta previa, feels that the hemoglobin, cell volume and red blood cell count do not always mirror

the true blood picture, and that these tests, though they may appear normal as indicated in the blood tests, may really represent hemoconcentration, while actually there is insufficient blood volume circulating in the vascular system. Taylor[14] and his group have emphasized the inability of the premature respiratory system to quickly reach a proper oxygen equilibrium in the external environment. This situation makes it mandatory not to further handicap the infant by added hypoxia due to insufficient blood volume because of blood loss.

CASE III. M.R., a 35 year old gravida III, para II, in her thirty-seventh week of pregnancy was admitted to St. Anne's Hospital on December 10, 1951, with painless vaginal bleeding. Intracervical vaginal examination revealed a marginal placenta previa. The bag of waters was ruptured artificially. The bleeding persisted. A laparotrachelotomy was done. The placenta on the anterior wall was partially under the vertical incision. It was lacerated, and then pushed aside. The infant was delivered immediately and was white and flaccid. The diagnosis was asphyxia pallida. It was resuscitated and placed in an incubator. Three hours later the diagnosis was changed to posthemorrhagic shock by a pediatrician who had had experience with a previous case. While a transfusion was being prepared the infant suddenly died. Autopsy revealed severe anemia of all the organs.

The case emphasizes the need for immediate differential diagnosis of asphyxia pallida from hemorrhagic shock, and the ruling out of erythroblastotic, hemolytic anemia. The latter is usually quickly done if the mother is Rh positive unless there is an O-A or other rare sensitization. The hypoxia of the anemia of hemorrhagic shock is different from anoxic anoxia of asphyxia pallida in that the infant suffering from the former breathes feebly and rapidly, may even cry weakly, may have a rapid heart beat, and may make slight body movements and have slight tone, depending on the severity of the shock, while the latter is characterized, not only by the paleness which is common to both, but by the absence of breathing and body tone, and slow heart beat. The exsanguinated baby does not respond to oxygen by a return of color, while the asphyxiated infant does after respirations have been established.

RUPTURES IN UMBILICAL VESSELS

Tearing may occur in cases of vasa previa, velamentous insertion of the cord, overstretching of the cord and thrombosis in a large vessel.

A vasa previa is an umbilical blood vessel which lies over the internal os as it courses through the fetal membranes unsupported by the cord or placenta; a velamentous insertion of the cord is usually a prerequisite, but it is possible that a blood vessel, (1) running to a succenturiate lobe or (2) between the lobes of a bipartite or multipartite placenta, or (3) an aberrant blood vessel might overlie the internal os and therefore be a vasa previa. Whether the woman is in labor, or the fetus is presenting by the head, or the vessel is near the placenta is not essential to the

definition. The vasa previa vessel or vessels may rupture before labor, at the onset of labor or at any time during labor—or not rupture at all. It may rupture before, at the time of or after the rupture of the membranes.

Of the fifty-two cases of vasa previa reported by Rucker and Tureman[12] from the world literature as of 1945, twenty-five cases resulted in stillbirths, while twenty-two cases resulted in survivals. In thirteen of these latter cases the vasa previa vessels were unruptured. In three cases the

Fig. 5. Vasa previa in twin pregnancy with rupture of vessel of the first fetus resulting in its intrapartum death from hemorrhage. Note anemia of placenta of first fetus composed with normal placenta of surviving second infant. (Courtesy of Dr. E. S. Groseclose.)

infants died shortly after delivery, eighteen hours after delivery, and a few days after delivery, respectively. The questions arise whether these babies could have been saved by immediate blood transfusions, and whether some of the surviving infants in the cases of the ruptured blood vessels might not have suffered from severe anemia which would have been benefited by giving them blood. Groseclose[4] reported a case of vasa previa in a twin pregnancy with a rupture of the vessels by the first fetus, resulting in its death from hemorrhage (Fig. 5). Kosmak[7, 8] reported two cases of fetal exsanguination: one due to torn vessels of a velamentous insertion of the cord entering the lower pole of a low implantation of the placenta (Fig. 6), resulting in intrauterine death of the fetus due to

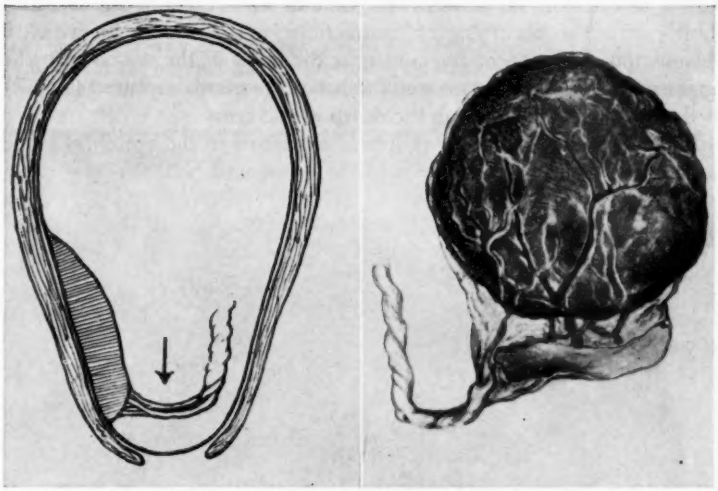

Fig. 6. Torn vessels of velamentous insertion of cord entering lower pole of low implantation of placenta. (Courtesy of Dr. G. W. Kosmak.)

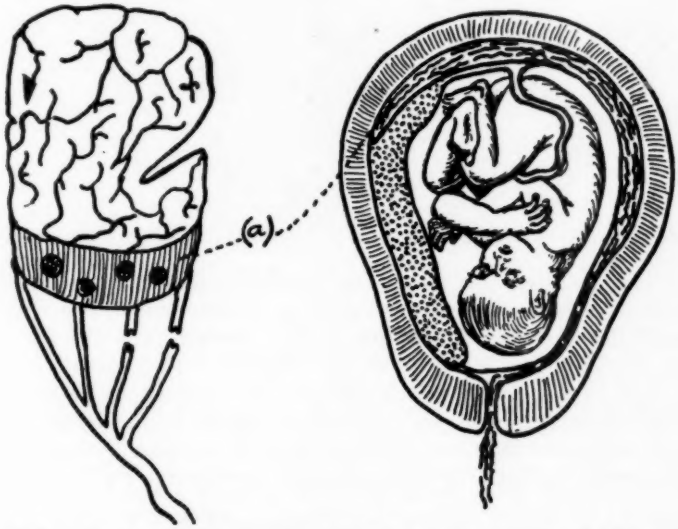

Fig. 7. Torn vessels of velamentous insertion of cord entering upper pole of normally implanted placenta. (Courtesy of Dr. G. W. Kosmak.)

tearing of velamentous vessels at the time of rupture of the bag of waters shortly after the beginning of contractions; and the other in which a velamentous insertion of the cord near the entry of the vessels into the upper pole of the placenta in the fundus of the uterus ruptured (Fig. 7) at the onset of labor, causing the death of the fetus.

In considering the broader problems of rupture of the umbilical blood vessels reference might also be made to Busby and Neal's[1] case of near-

Fig. 8. Illustration of rupture of small vein at marginal insertion of cord (arrow).

fetal exsanguination due to the mechanical tear of a small vein at the marginal insertion of the cord as a result of overstretching of a short cord around the fetal neck at the time of the expulsive efforts of delivery (Fig. 8). The infant was saved by the immediate transfusion of 136 ml. of whole blood (type O, Rh negative, female) into the umbilical vein.

Leff[9] reported a case in which there was a rupture of a placental blood vessel which had thrombosed on the fetal surface near the cord with posthemorrhagic death of the fetus before the delivery (Fig. 9).

CASE IV. RUPTURE OF A VASA PREVIA WITH POSTHEMORRHAGIC SHOCK IN THE INFANT. M.McC., a 27 year old gravida II, para I, Rh-positive mother, was admitted to Loretto Hospital on November 1, 1948, having uterine contractions. Just before delivery the vaginal examination revealed the cervix to be 7 cm. dilated, the head well engaged, and the bag of waters bulging. This was ruptured, with a resultant rush of amniotic fluid, which was distinctly red in color. A few minutes later a

female infant was delivered spontaneously. She appeared pale and listless. Respirations were rapid and shallow, and the cry weak. The limbs had little tone, and the liver and spleen were not palpable. The placenta was bipartite, with the vessls to each lobe of the placenta running unsupported through the membrane for the last 16 cm. from the umbilical cord. Several of these vessels traversed the membranes in

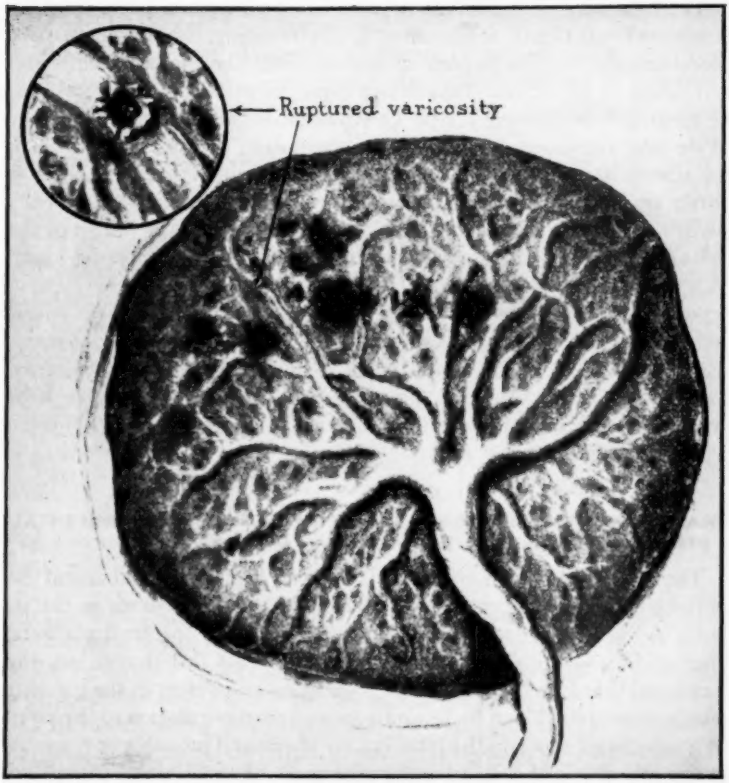

Fig. 9. Rupture of thrombosed vessel on fetal surface of placenta. (Courtesy of Dr. M. Leff.)

the immediate region of the artificial rupture of the membranes, but a tear in these vessels was not apparent. Because of the reddish amniotic fluid and the character of the placenta, a diagnosis of posthemorrhagic shock in the infant was entertained. While preparations were being made to give blood to the infant, it suddenly died. The autopsy was not remarkable except for severe anemia of all the organs.

This case emphasizes the need for immediate decisive therapy once the nature of the case is grasped from a quick examination of the placenta, and the memory of the gush of the red amniotic fluid at the time of the rupture of the bag of waters. No time should be wasted for any

laboratory examination of the extent of the anemia when the infant is in severe posthemorrhagic shock.

Treatment

The treatment of the infant suffering from posthemorrhagic shock of a ruptured vasa previa, as presented in the foregoing, is a simple, massive blood transfusion. The hypoxia of anemia should be combated with oxygen, while 70 ml. of blood are drawn from the mother if she is positive, or from the department's type O Rh-negative blood supply with the Witesbsky substance, for immediate transfusion of the infant through the umbilical, medial malleolar, saphenous or temporal vein. If there is strong reason to believe that the infant presents a posthemorrhagic shock picture, a transfusion of 10 ml. of blood per pound of body weight of the infant should not harm the baby while a final evaluation is being made. When the posthemorrhagic anemia is short of severe shock, the proper type and cross-matched blood can probably be awaited. Busby and Neal[1] recommend the umbilical vein as the best route to institute therapy, using a no. 17-gauge Diamond polyethylene catheter which is inserted for 3 to 3½ inches. Blood is drawn in 10-ml. aliquots from a bottle of type O, Rh-negative, female blood by an enclosed system, and injected into the infant.

UNAPPARENT HEMORRHAGE FROM THE FETAL SURFACE OF THE PLACENTAL-UTERINE JUNCTION INTO THE MATERNAL CIRCULATION

The third part of this paper deals with an interesting and recent hypothesis of occult placental hemorrhage with resultant shock in the infant, which is postulated to occur from a break in the fetal placental circulation into the maternal circulation. This was first recognized, and a case published, by Wiener.[16] His postulation of a defect in the placenta which allows fetal blood to flow into the maternal circulation to the point of hemorrhagic shock in the fetus is a novel one and probably as plausible as the hypothesis of such a break as the cause of sensitization in erythroblastosis. In fact, the case given by Wiener was an example of mild erythroblastotic hemolytic anemia with a superimposed posthemorrhagic anemia—both caused by such a placental leak.

To quote Wiener[16] in the discussion of his case: "The simplest way to account for the findings in this case would be to postulate some defect on the fetal side of the placenta. Moreover, a slow ooze of the fetal blood from such a placental defect would also account for the extreme anemia, and shock-like condition of the infant at birth. The main objection to this concept is the difficulty of demonstrating such postulated placental defects in pathologic specimens. However, the reason for this may be that such defects need not be large, and as a rule would probably be

demonstrated only in vivo, as we succeeded in doing in another case recently seen by us. In this other case, the baby was delivered by Cesarean section, and at the operation a herniation was found of the anterior uterine wall (due to a previous Cesarean section) consisting of a sac about the size of a walnut, and lined only by peritoneum and filled with blood which ruptured upon palpation."

To further support Wiener's hypothesis of fetal bleeding into the maternal circulation are the following observations. Kline,[6] in an extensive study of normal and erythroblastotic placenta, demonstrated micro-

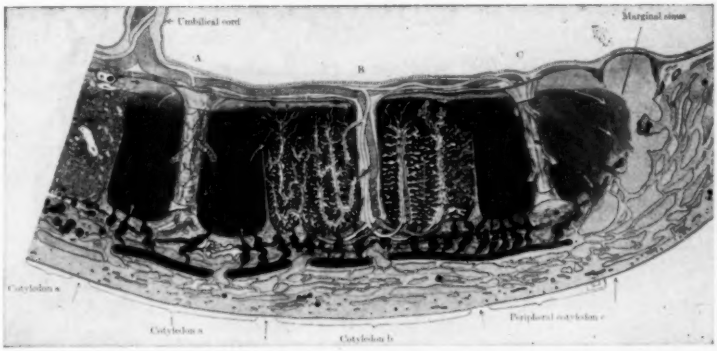

Fig. 10. Drawing illustrating cross section of placental uterine junction. (Courtesy of Dr. Greenhill, from DeLee and Greenhill: Principle and Practice of Obstetrics. Adapted from Spanner.)

scopically the presence of such leaks in the capillaries, villi and trunks into the intervillous spaces. Bartolmez, in a discussion of Romney and Reid's[11] corrosion and injection studies of the placental circulation, pointed out the ability of the intervillous spaces to take up the amniotic fluid, as evidenced by the case of the late Dr. E. Cornell in which he (Bartolmez) cut across the intact uteroplacental junction of a five month pregnancy and opened into the intervillous sinuses containing clear amniotic-like fluid. He felt that the replacement of the amniotic fluid about every three hours took place through the mechanism of transudation through the amnion and chorion into the intervillous spaces. He argued that during labor the amniotic fluid would probably be completely pumped out of the maternal intervillous spaces with every two or three contractions of the uterus.

Similarly, one may postulate that late in labor only a traumatic break in the distal zone of fetal capillaries into the maternal intervillous spaces is necessary to account for considerable fetal blood loss into the mother's circulation. Such blood would be pumped into the marginal sinuses and uterine venules of the mother with each contraction.

The fact that many more infants are not born with the anemia of blood loss probably can be explained on the ground that the usual microscopic leaks as described by Kline[6] are not the mechanism in these cases, and that the slow ooze postulated by Wiener is probably not the pathologic condition here. It may be that posthemorrhagic shock in the fetus is due to a sudden traumatic, unusual break in the fetal capillaries, villi and trunks during labor with considerable blood loss into the maternal circulation.

Wickster[15] has presented another hypothesis which would also explain such blood loss. One might conjecture that toward the end of labor a traumatic leak in the villi and the distal zone of the short capillaries and the vascular trunks would allow extravasation of blood into the decidual plate of the uteroplacental junction. Enough blood, for example, 80 ml., could be stored here to cause shock in the fetus and remain until the placenta is separated after delivery. The blood so stored would be easily mistaken as part of the normal third-stage bleeding as the placenta separated, yet it would be sufficient to cause posthemorrhagic shock in the newborn.

Case V. R.C. a 34 year old gravida II, para I, was admitted at term to Loretto Hospital on December 29, 1948, in active labor. She was Rh negative, and her husband Rh positive and heterozygous. The first child was Rh negative. There were no previous blood transfusions. Diamond tests taken during her first pregnancy and present pregnancy revealed no antibodies. Her last Diamond test of November 24, 1948, was negative. The nurses' notes 20 minutes before delivery read: "Fetal heart tones fade out, 80-148, quality poor." She was delivered of a 6 pound, 6 ounce male infant after a labor of 3½ hours.

The baby was pale and listless. It breathed weakly and rapidly, and did not cry. The liver and spleen were not palpable. Two pediatricians who saw the infant felt that he was in poor condition and probably would not survive with any type of treatment. Because the mother was Rh negative, and the infant in anemic shock supposedly from the hemolysis, a diagnosis of severe erythroblastotic anemia was made. It was felt that, despite the fact that the usual findings of enlarged liver and spleen and early jaundice with such a marked anemia of hemolytic origin were not present, the absence of these did not rule out this diagnosis. An exchange transfusion was given the infant, using Rh-negative, type O blood, which was available. Specimens of the infant's blood before, during and after the transfusion were sent to the Samuel Deutsch Serum Center for analysis along with a specimen of the mother's blood. Five hundred milliliters of blood were given to the infant through the medial malleolar vein, and 375 to 400 ml. of blood were simultaneously withdrawn from the umbilical artery. The infant responded dramatically to the treatment, continued to do nicely during the hospital stay and has continued to do well to the present.

After the transfusion we learned the results of the tests on the mother and infant. The mother had no saline or blocking antibodies in her blood, and neither did the infant. The infant was Rh positive. The icterus index of the infant's serum was normal. The original count on the infant before transfusion was red blood cells, 3,680,000; hemoglobin, 13.5 gm.; polymorphonuclears, 6170; lymphocytes, 38 per cent. The differential count revealed polychromasia with 5 nucleated red blood cells per 100 white blood cells counted. All this supported a diagnosis of hemorrhagic anemia, but there was no obvious basis for such a loss of blood from the fetus except through the placenta, and no abnormal condition seemed to involve it. (1) Labor had been normal with no signs of vaginal bleeding; (2) there was no undue rigidity

of any part of the abdomen between contractions; (3) the delivery was attended by a normal blood loss before and after the birth of the infant and placenta; (4) the placenta itself had a normal appearance.

Another possibility might be the loss of blood retained in the cord and placenta since we did not (1) give ergotrate with the shoulders, (2) wait for the cord to stop pulsating before clamping it, (3) strip the cord. None of these procedures was done because of the fear of an erythroblastotic infant being born. However, despite the fact that these steps might have given the infant an additional 30 to 90 ml. of blood, it is not probable that the severe grade of anemia in this case could be accounted for by failure to do them, since the infant appeared to be embarrassed before the delivery, as indicated by the irregular fetal heart tones.

This case seems even more clearly to support the hypothesis of the possibility of occult placental hemorrhage from the fetal circulation defect than Wiener's case, since the infant had only posthemorrhagic anemia. One could conjecture that the bleeding from the defect in the fetal circulation directly entered the maternal circulation in quantity enough to cause shock, e.g., 80 ml., but not over a long enough period to cause sensitization. In fact, such bleeding into the maternal circulation need never cause sensitization in the mother, since it is well recognized by hematologists that many Rh-negative women can be given repeated injections of Rh-positive blood without antibodies developing. This was apparently the case here, since follow-up studies many months later never did reveal antibodies.

COMMENT

Not infrequently in making the differential diagnosis of posthemorrhagic anemia with shock in the newborn there is little time for the pediatrician to verify the diagnosis and carry out the emergency treatment. The obstetrician must immediately grasp the situation and institute the blood transfusion, occasionally directly from the mother. He should be as familiar with the immediate treatment of infant hemorrhage emergencies as he is with the hypoxic emergencies. In fact, even if a pediatrician is present, it is the obstetrician who has followed the labor and delivery and has recognized the abruptio placentae or placenta previa or cesarean section incision into the placenta with the consequent possible blood loss as well as the more common asphyxia to the infant. Likewise, in the case of vasa previa and other hemorrhages from the umbilical vessels, it is the obstetrician who, on seeing the poor condition of the infant and noting the typical velamentous insertion of the cord with vasa previa, must correlate the pathology and tell the pediatrician what to do. Pediatricians readily admit that until this condition of posthemorrhagic anemia with or without shock in the infant is more widely written

about, and its causes discussed, valuable time may be wasted while they are arriving at a diagnosis, which the obstetrician is in a better position to make. Especially is this true in the Rh-negative mother, in whom the possibility of a severe erythroblastotic hemolytic anemia must be differentiated. Interestingly enough, it was not a pediatrician or an obstetrician, but a hematologist who sensed the need for and emphasized the definitive treatment of the infant in these cases.

Fletcher's[3] and Taylor's[14] recent articles on premature infant hypoxia are stimulating further interest in the more approved methods of immediate treatment of the hypoxic infant, and this should be paralleled by a growing interest in the possible need for blood in the embarrassed infant—not only in the infant in severe hemorrhagic shock, but also the infant in the past who survived varying degrees of anemia which went unrecognized or untreated—moderate anemias which, if treated, might have hastened a better early adjustment of the infant to its environment.

Every premature infant born of a case of placenta previa, abruptio placentae, cesarean section incision into the placenta, or abnormal placenta should be followed by repeated hemoglobin, cell volume and red blood cell counts.

When a physician is confronted with a premature newborn in shock, the following should be done:

1. The infant is immediately placed in an incubator in which heat, humidity and oxygen are controlled.

2. Blood should be stripped from the umbilical end of the cord, if possible, and placed in two test tubes (one oxalated) for the routine tests ordinarily done on potentially erythroblastic newborns, viz., hemoglobin, red blood cell differential, icterus index or bilirubin, type, Rh factor, and cross matching, and Coombs test as needed.

3. The transfusion in a premature is usually best given through the umbilical vein with a no. 18- to 20-gauge Diamond polyethylene catheter or metal tube which is inserted for 3 to 3½ inches. A venesection on the ankle, wrist, antecubital fossa or scalp vein may be formidable in the premature because of the small size and caliber of the vessels. Bone marrow infusions through the anterior tibial plateau are probably less difficult, but there is the possibility of infection and trauma. A 1-cm. short bevel needle is used.

4. The blood to be transfused must not be cold. The first 10 ml. of the venoclysis may be given rapidly because of the blood loss, i.e., within ten to fifteen minutes, but the subsequent amount should be allowed to flow at twelve to fifteen drops a minute. In the bone marrow transfusion the rate of infusion is usually governed by the small marrow cavity and the paucity of vessels carrying blood from the marrow cavity to the systemic circulation.

5. The amount of the venoclysis should be limited to 10 to 12 ml. per

pound of body weight to prevent as much as possible the overloading of the cardiovascular system. This may be repeated in twelve hours.

6. In severe cases of posthemorrhagic anemia and shock the blood should be taken from the obstetrical department's type O, Rh-negative blood with Witebsky substance and given immediately to the infant as outlined earlier. If there is no type O, Rh-negative blood available and the mother is Rh positive, the needed amount of blood should be immediately drawn from the mother and given to the infant. If there is no type O, Rh-negative blood available and the mother is Rh negative, plasma should be given until Rh-negative blood is secured.

7. When there is time, the infant's blood status should be evaluated by the hemoglobin and other blood determinations, and the needed amount of the proper type and Rh-factor blood given.

8. In exchange transfusion for a severe hemolytic erythroblastic anemia, 30 to 70 ml. more of blood should initially be given than are withdrawn to protect against a possible superimposed hemorrhagic anemia.

CONCLUSIONS

1. The role of posthemorrhagic shock in the death of the newborn premature in cases of placenta previa, abruptio placentae, cesarean section incision into the placenta, and ruptures of the umbilical vessels is re-emphasized.

2. The abnormal architecture of many of the placentas in placenta previa is pointed out. The thin, wide, lobulated placentas which often have a marginal or velamentous insertion of the cord predispose to rupture of the fetal vessels in the cotyledons in the tearing mechanism of the development of the lower uterine segment in the third trimester and during labor. A case is presented which illustrates the possible danger to the fetus of the labor contractions and the intracervical vaginal examination in the presence of such a placenta.

3. Two cases of cesarean section incision into the placenta with resultant posthemorrhagic shock in the newborn are discussed in detail. The differential diagnosis from erythroblastic anemia and asphyxia pallida, and the differences in treatment are noted. Recommendations are made for minimizing blood loss with the anteriorly implanted placenta.

4. Cases are cited in which rupture of the umbilical blood vessels occurred in vasa previa, velamentous insertion of the cord, overstretching of the cord, and thrombosis of a large umbilical vessel. A case of ruptured vasa previa with posthemorrhagic shock in the newborn is related, and the importance of immediate definitive therapy with transfusion emphasized.

5. A case illustrating Wiener's[16] new hypothesis of occult bleeding

from a break in the fetal circulation into the maternal circulation as a cause of severe anemia due to blood loss in the newborn is discussed. Certain observations supporting this postulation are advanced. An alternate theory is presented.

6. A plan is suggested for the management of posthemorrhagic shock in the newborn premature.

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FACTORS INFLUENCING PREMATURE MORTALITY

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When a pediatrician is entrusted with the life of a premature infant, he is immediately confronted with the vital question: What are the chances for survival? Unfortunately, while we are quite aware of the many hazards that such a child will encounter and can proceed with the best knowledge at our command to counteract these difficulties, we cannot evaluate the inherent vitality of its germ plasm. This might be more bluntly stated as the ability of the child to grow. This is characteristic of each individual infant, and must be evaluated accordingly. There are, however, some definite factors that greatly determine premature mortality and, if known and guarded against, will aid our ability in a more definite prognosis. These factors are as follows:

1. The degree of development or immaturity of the infant at birth. This is perhaps the first and greatest cause of mortality, since all the other causes indirectly lead back to its birth condition. This is also somewhat influenced by the race and sex of the infant and multiple birth.
2. Type of birth. This is influenced again by the age and parity of the mother, the complications of labor, and type of delivery.
3. Congenital malformations, if present, or, if present, such as can be satisfactorily overcome.
4. The medical and nursing care of the premature infant during that period until it can make its own adjustments. This includes establishing satisfactory respiration, temperature adjustment, feeding and formulas that are satisfactory to each infant, and guarding against infection.

DEGREE OF DEVELOPMENT OR IMMATURITY

It is frequently difficult to determine the exact time at which birth should occur, and to evaluate immaturity from this knowledge. When

a birth weight of 2500 gm. (5 pounds, 8 ounces) or less is taken as evidence of prematurity, the mortality has been found to be inversely proportional to the birth weight. Dunham[8] has collected statistics from various hospitals that show that from 2001 to 2500 gm. the percentage of survival is at least 93 per cent, from 1501 to 2000 gm. it is at least 82 per cent, from 1000 to 1500 gm. it is at least 50 per cent, and under 1000 gm. it is from 0 to 10 per cent. Though the exact percentage of mortality will vary from year to year, this will be found to be substantially correct. Dunham puts this in excellent terminology for parents by stating that in the higher group the prognosis is excellent, for the 1501 to 2000 gm. group it is good, for the 1000 to 1500 gm. group it is fair, and for under 1000 gm. very poor.

In using the birth weight as an estimate of fetal life prognosis, plurality of births may have some effect on these percentages. Peckham[19] in 4055 infants weighing less than 2500 gm. at birth found that the chances for survival were much greater for twins than for single-born infants in each 500-gm. weight group. He quite properly states that this is only an indication of the closer approach to maturity at any given weight of twin infants as compared to single-born children. Similar findings were those of Dunham and McAllenney,[9] who also state that many multiple births are close to term or even at term, with a low birth weight, but having a longer period of gestation than single-born infants of the same weight, and that the infants are more mature and better prepared for extrauterine life.

In gross mortality statistics there is a difference in premature mortality between males and females, males having the greater mortality. Duffield[7] and associates in a study of over 100,000 live births in New York found the mortality of male premature infants whose birth weight was under 2500 gm. to be twenty-four per 100,000, as compared to only eighteen females per 100,000. This is even more accentuated when it is realized that according to Peckham[19] the percentage of white premature infants born is 100 male to 110 female. The preponderance of female premature infants born may be to a great extent due to the relatively smaller birth length and birth weight of the female child.

TYPE OF DELIVERY

Though it has long been assumed that the age and parity of the mother would affect the viability or prognosis of the premature infant born to her, there is really little evidence that this greatly influences these results. Breese[2] found that, in almost a thousand births analyzed, unless the age of the mother was over forty years, there was little evidence that it was a factor. He did find that in women over forty years of age there was a

slight increase in mortality that was more than could be accounted for on a basis of the infant's weight.

In two studies that have been made on the influence of the type of delivery on mortality, Peckham[19] found that, excluding breech delivery, there was no particular difference in the various types of delivery. He did emphasize, however, that in many operative conditions the choice of delivery was dictated by some maternal abnormality such as heart disease or placenta previa. In such instances the mortality would be that of the maternal complication rather than of the type of delivery.

On the other hand, Miller[15] found that infants born after cesarean section showed a higher mortality than those born spontaneously or by low forceps. He does emphasize that this again may be due to the greater proportion of premature infants weighing less than 1500 gm. born by this method, and that the mortality is determined almost entirely by birth weight.

Though almost all authors find that breech delivery of the premature infant carries the highest mortality of all operative procedures, this again may be due to the fact that the earlier in pregnancy labor occurs, the more likely the infant will be delivered by breech extraction. Beck[1] believes that the danger is from the cervix being insufficiently dilated by the shoulders of a small baby and not sufficiently large enough to permit a safe passage of the head. This is especially true of infants of less than 2000 gm. birth weight. In his series reported 70 per cent died between 1000 and 1500 gm., and 50 per cent between 1500 and 2000 gm. He concludes that spontaneous delivery with episiotomy, if necessary, is the safest manner of birth for the premature infant.

Dieckman[6] reports that the incidence of breech presentation in premature infants of twenty-eight to thirty-six weeks' gestation is from 20 to 40 per cent, compared to 4 to 5 per cent for full term infants. The gross mortality average for full term infants delivered by breech is 7.7 per cent, compared to 25 per cent for premature infants. This again points to the fact that the earlier labor occurs, the more likely will the infant be in a breech position, which again means that such will not have the handicap of the type of delivery, but will have the added handicap of a lower or almost nonviable birth weight.

Will better obstetrical care result in a significant lowering of premature mortality? The comments of Brooks[3] are of interest. He believes that there will be no decline in mortality rate of premature infants born in hospitals, because more infants will be born alive that formerly might have resulted in miscarriages. Furthermore, the birth of larger babies will be delayed, and they will be more viable and not come into premature classification. A larger number of small babies will be born that

previously were not carried to the point of viability, with a corresponding greater likelihood of increasing mortality.

CONGENITAL MALFORMATIONS

The third of the factors that influence premature mortality is congenital malformations. Though there is some difference in published data, the majority opinion is that they are more frequent in the premature infant than in the full term one. Wallace and Baumgartner[25] state that in New York in 1951, 1501 infants were reported to have been born alive with one or more congenital malformations, an over-all reported incidence of 9.2 per 1000 live births. The incidence in the premature group was 18.2 per 1000 live births, as compared to the mature group of 8.3 per 1000 live births. This is over twice as many.

Obviously, a congenital deformity occurring in a premature infant would be of greater handicap to its existence than in a full term infant. In the same study the neonatal mortality rate in the prematurely born group with reported congenital malformations was 372 per 1000 live births, or three times that of all prematurely liveborn infants in the city. This neonatal mortality rate in the prematurely born group was four times that of the full term group.

As time goes on we are becoming more aware that environmental factors play a much greater part in congenital malformations than was ever supposed. It is now known that radium and roentgen irradiation during pregnancy arrest growth of the offspring. Rubella, if contracted by the mother in the first trimester of pregnancy, can result in defective children. For this reason it might be well to encourage the contraction of the disease before the childbearing age. Other viral diseases have been cited, but as yet there is no real proof.

Toxoplasmosis, although rare as a maternal infection, may cause congenital defects. This may be transmitted to the fetus in utero. Symptoms of the nervous system may be present at birth or appear in a few days or weeks after birth.

Infants of mothers with diabetes, according to White,[28] show a higher incidence of congenital malformations than those of normal mothers. These are usually of mesenchymatous tissue. Joslin[13] reported an incidence of 17 per cent in 125 such infants.

Much thought has been given to the effect of maternal diet since Warkany[26] was able to produce a variety of congenital defects in animals when depletion of a maternal specific nutritional factor was accomplished. Though such conditions have not been produced in human beings, it certainly gives one pause as to the effect that poor diets might have on the offspring.

The practical implications of all this work are best summed up by

Parmelee[18] in the statements that they prove that at least some congenital anomalies are not completely beyond the possibility of control, and they dispel some of the mystery of malformations in cases in which no hereditary taint is apparent. This is valuable to the physician called upon to discuss the matter of a malformed child with the parents.

Most abnormalities are not apparent until after birth, and many may not be apparent even at this time. It is the duty of the physician to inspect and evaluate all abnormal actions and appearances of the newborn infant, for his responsibility lies in an early diagnosis of those conditions that may be treated.

Nervous System

The greatest incidence appears to be in the nervous system. This has been reported as from 37.5 to 60.5 per cent.[17] The most frequent is *hydrocephalus,* to be suspected if the head measurement is over 33 cm. with a rapid rate of increase, bulging fontanels and separate sutures. These are frequently associated with *spina bifida.* These conditions are individual and should be judged accordingly. Consultation with a neurosurgeon should be sought at once, and his opinion and the various individual factors involved should have precedence. Though it is true that many of these operations are unsuccessful, the child should be given the full benefit of whatever measures might best serve the case.

Gastrointestinal Tract

The next most frequent body system to be involved is the gastrointestinal tract. Anomalies of the gastrointestinal tract have the three cardinal symptoms of vomiting, distention, and either absence or change in normal color of the stool. These are always grave danger signals and deserve prompt attention.

Esophageal vomiting indicates a malformation, usually an *atresia* or a *tracheo-esophageal fistula.* It may be suspected at once by an excess of saliva accumulation in the mouth, and usually associated cyanosis. When fluid is given, vomiting, choking and cyanosis occur at each instance. Confirmatory diagnosis may be made at once by the failure of a catheter to pass down the esophagus. Roentgenograms will show the catheter in the pouch, and 1 or 2 cc. of iodized oil introduced will show up a fistula in lateral roentgenograms. An opaque medium such as barium should not be given. If there is an intestinal pattern with a blind upper sac, the condition is an *esophageal atresia* with the fistula between the lower segment and the trachea. Ninety per cent of these will fall into this category. If there is no pattern, there is no fistula. Ladd[14] emphasizes that a delay of longer than twenty-four to thirty-six hours carries a marked

rise in mortality. Successful reports have been made of such operations on premature infants. Prompt diagnosis and immediate operation are essential if life is to be saved.

The most frequent causes of malformation of the intestines are *atresia* and *stenosis*, with the less frequent malrotation, Meckel's diverticulum and meconium ileus. Stenosis is most frequent in the duodenum, and atresia in the ileum. This has the greater mortality, while stenosis has a better prognosis, especially if located high up in the intestinal tract.

The most important diagnostic factor in any of these obstructions is vomiting. Pyloric or duodenal vomiting due to obstruction at either of these levels of the small intestine is explosive and contains stomach contents. Obstruction at a still lower level, either of the small intestine or large, may be delayed in its onset, but is usually preceded by distention at the point of atresia. This is an important sign. If bile is present in the vomitus, the obstruction is below the ampulla of Vater. If the obstruction is in the lower ileum or the colon, fecal material will eventually be vomited.

It must be remembered that meconium may be passed even if obstruction is complete. Fecal material may be passed through the bowel or not at all, depending on the extent of the obstruction. If the obstruction is above the ampulla, the stools will be normal meconium. If it is below the ampulla, they will be gray, white and mucoid. The character of the meconium is of importance; if on microscopic examination no cornified epithelial cells are seen, the obstruction is complete, since amniotic fluid which contains these cells has not been passed (Farber test).

The greatest help in the early diagnosis of these conditions has been made by the studies of Wasch and Marck.[27] In roentgenographic studies of the normal newborn they found that air is present in the stomach at birth. Between the first and third hours the small bowel is filled, and by the eighth hour closely packed segments of the small bowel fill the abdominal cavity. At the end of the twelfth hour the normal pattern is established. This makes a contrast medium unnecessary and is much safer for the infant.

Early operation may now be successfully accomplished and is lifesaving for the infant. Preoperative treatment to combat dehydration, prevent hemorrhage and conserve body heat during operation is of great importance. Though the operative mortality in these conditions is high, they are incompatible with life, and early diagnosis and surgical treatment are becoming more successful.

Atresia or *stenosis* of the *anus* or *rectum* is uncommon. Diagnosis can be made by an absence of anal opening, or abnormal peritoneal opening, symptoms of acute obstruction unless fistulas are present, and roentgenograms with the head down in which the gas in the intestines outlines the rectal pouch. The treatment is surgical and depends on the type of

anomaly. If the fistula is low, correction is usually done in the first days of life; if high, treatment is delayed, according to Ladd and Gross.[14] With no fistula present, complete obstruction occurs, and operation must be immediate, even though this is usually associated with other congenital anomalies.

Anomalies of the biliary tract are shown by jaundice which is present at birth or shortly after, clay-colored stools and bile-stained urine. The liver and spleen may be enlarged. According to Hsia,[12] in about one half of these children the cause is congenital atresia of the bile ducts. In about one quarter it is due to inspissated bile following erythroblastosis neonatorum, and in the remaining one quarter, to inspissated bile caused by conditions of unknown etiology. This has changed our conception of these conditions as a surgical emergency. In the inspissated bile group, practically all instances due to erythroblastosis will recover with appropriate treatment, and 80 per cent of the group due to unknown etiology. Both groups have a much greater mortality if exploratory operation is done. Clifford[5] states that most physicians now advise waiting at least two months before surgical exploration is attempted. True atresia can usually be diagnosed by this time by the absence of bile passing through the intestine, no urobilinogen appearing in the urine, and a general upward trend of the serum bilirubin.

The last condition that requires immediate diagnosis and surgical repair is *diaphragmatic hernia*. This may be suspected by transient or persistent cyanosis relieved by changing the infant's position, vomiting and dyspnea. The diagnosis is confirmed by a flat plate of the thorax, and anteroposterior and lateral views. This will show thoracic gas shadows arranged in an intestinal pattern. Barium should not be used, since it increases the danger of vomiting and aspiration pneumonia. Ladd and Gross[14] recommend operation within the first forty-eight hours, since the intestine is not yet fully distended. Delay may result in sudden death.

Cardiovascular System

Congenital malformations of the heart are as frequent in the newborn period as those of the gastrointestinal tract. They are rather difficult to diagnose, however, and as yet are not surgically attempted in the newborn or premature period. I believe that they will be, and for this reason give attention to three anomalies not compatible with life, of frequent occurrence among the cardiac anomalies, and surgically correctible in older infants.

The first is *double aortic arch*. Here the trachea and esophagus are encircled by a vascular ring. The symptoms are stridor, which comes on in the first day of life, a barking metallic cough and difficulty in swallowing. A barium swallow reveals under the fluoroscope a narrowing of the

esophagus at the level of the aortic arch, and indentation of the posterior surface of the esophagus in the lateral view. The symptoms are alarming and often fatal. The operation consists in severing the smaller portion of the arch.

The second is the infantile type of *coarctation of the aorta*. Here the aorta is narrowed from the origin of the left subclavian to the insertion of the ductus arteriosus. If there is cyanosis from some other anomaly, the condition may be suspected. The femoral arteries may be palpated in some instances. The blood pressure in the upper extremities is usually high, but low in the lower extremities. Calodney and Carson[4] diagnosed fourteen of twenty-two instances of this condition. This condition is not compatible with life after the closure of the ductus, which may take place at any time.

The third is *tricuspid atresia* or *stenosis*. The type amenable to surgery consists of the foregoing plus interatrial communication, hypoplasia of the right ventricle, an atresia of the pulmonary artery, and a patent ductus or interventricular septal defect. These children always have cyanosis, systolic murmur, large left ventricle shown by roentgenogram, and left axis deviation by the electrocardiogram. This is not compatible with a long life span. We have had two such full term infants that survived operation done at one month of age.

MEDICAL AND NURSING CARE

The fourth large group of conditions that influence premature mortality and the one in which most advances have been made in the last few years is the medical and nursing care of the premature infant during that period until it can make its own adjustments. These are establishing satisfactory respiration, temperature adjustment, feeding, and guarding against infection. These are discussed more in detail in other articles in this symposium, and will be only briefly reviewed here.

Establishment of Respiration

Asphyxia is one of the most important things that we have to contend with. The problem of obtaining proper breathing is under two handicaps. The first is inability of the respiratory center to function. Various types of resuscitators have been used, but none are entirely successful. We have been trying phrenic stimulation similar to that used in bulbar poliomyelitis.[23] This has not been entirely successful. Though a good mechanical stimulation can be attained, it becomes useless unless the center itself will take on the work. Nothing else remains except clearing the child's air passages and giving unlimited oxygen.

The second cause of difficulty, and by far the greater, is in the lung

itself. The first problem is *atelectasis*. Occasionally this may be localized to one or two lobes from obstruction of a large bronchus. This should be suspected in all instances of cyanosis occurring at once or shortly after birth. It is necessary to rule out other causes of cyanosis such as congenital heart disease, intracranial hemorrhage, pulmonary infection, tracheobronchial fistula, diaphragmatic hernia and adrenal hemorrhage. This may be accomplished by a roentgenogram of the chest, and is obvious if the fluoroscope indicates a lung density.

We have made it a practice to fluoroscope all our premature infants immediately after birth, and if such a condition exists, a bronchoscopist is called into consultation. The method used is insertion of an infant-sized bronchoscope as suggested by House and Owen.[11] Even if only the main bronchus leading to a lobe is cleared, spontaneous drainage will follow in twenty-four to forty-eight hours.

This method is useless if the atelectasis is scattered over the lung area, or more than a single lobe is involved. In these instances we must resort to oxygen alone, or some form of mechanical resuscitation, which is not entirely satisfactory. A new approach to this problem was first shown by Miller,[15] who used a humidified atmosphere which contained a material that acted directly on the substances blocking the airways. The detergent we have been using is Alevaire, or Triton WR 1339. This is administered in an apparatus as outlined by Ravenel,[20] consisting of a nebulizer attached to an oxygen tank. The vapor is delivered directly into a croup tent or the incubator.

We have been using these measures for the past year. Nebulization is easy to administer, and does not seem to have any injurious effects. It is our impression that it is helpful. We have had some deaths from massive atelectasis, showing that it is not the complete answer to this condition, but it certainly offers at least a sensible method of approach.

Pulmonary hyaline membrane is a main factor in deaths from respiratory causes in the newborn period. Miller[15] believes that it is a protein exudate from injured tissues of the bronchioles and alveoli. The symptoms begin two to three hours after birth, following normal breathing, with dyspnea, retractions of the costal margins and lower sternum, and grunting followed by cyanosis. Death occurs within a few hours after onset in many instances, while in others the condition persists for two to four days with recovery. We have been using Alevaire when these symptoms arise, and believe that it is beneficial.

Temperature Adjustment

The inability of the child to maintain body temperature is an important factor, but one that has been very well met in the last few years. The type of incubator is immaterial as long as the baby is kept at opti-

mum temperature. The baby should be easily accessible and easily seen at all times. It is also essential to use an incubator that has a spark-proof thermostat approved by the underwriters. The baby should be kept in the incubator until it can hold its own temperature. This may be any time after it has attained a weight above 4½ pounds.

Feeding

While the feeding of the premature infant is one of the most important phases in its development, knowledge of food and fluid requirements is generally applied, and has undergone no marked change in the last few years. This all sums up to the statement that any good feeding in the hands of a competent pediatrician is satisfactory. I must admit that I prefer human milk. However, in a recent round table on prematurity, of the thirty-nine pediatricians present only six used human milk. We obtain this from maternity mothers, wet nurses or the premature's mother. It is frozen and stored in a deep freeze. It can be used as long as a year with safety.

How often should the premature infant be fed, and how soon should it be fed? We have felt that it is a mistake to begin feedings too soon on these infants. Certainly in this way we never have any edema in our infants. We wait forty-eight hours or longer. As to the time between feedings, we use the four hour interval, although again this is immaterial. The method of feeding depends on the training of the personnel and the ability of the baby to suck. We gavage them at four hour intervals until the weight is about 4 pounds; then the nurse begins bottle feedings.

The polyethylene nasal catheter, as suggested by Royce,[21] appears to deserve serious consideration. In hospitals that do not have personnel trained in gavage feedings, I have found it to be entirely satisfactory. It obviates the necessity for frequent passing of a gavage tube.

As to accessory fluids, a great many will give 5 per cent dextrose or normal saline solution between feedings. In studies we made over a ten year period we found that 5 per cent carbohydrate suppresses the amount of feeding these children would take, by suppressing hunger. We give only water by dropper between feedings, as much as the baby will take, and do not have to use intravenous or subcutaneous fluid injections. In case of vomiting or diarrhea, fluids are given as conditions demand.

Besides food and fluids, the premature needs around 20,000 units of vitamin A daily. This seems to be absorbed better in water-soluble form. Vitamin B is not necessary. Vitamin C is necessary for oxidation of amino acids as well as against scurvy. The vitamin D need is around 400 units a day according to Glasser,[10] and the administration of 400 to 800 units is adequate and safe.

Vitamin K is still given in many clinics as a routine procedure, since it

has been thought that the premature infant has a longer prothrombin time than the full term infant. Studies that we[22] have made show that the decrease in prothrombin content of the blood is similar to that of the full term infant, and, as in the full term infant, this can be increased by the administration of vitamin K. However, this had no effect on hemorrhagic manifestations, which were 9 per cent as compared to 6 per cent in the full term infant. There were no instances of cerebral hemorrhage in the group not given vitamin K, while there was one instance of cerebral hemorrhage in the group to which it was administered. This simply demonstrates that capillary fragility is an important factor in the premature infant and that the administration of vitamin K does not materially affect the hemorrhage after it has once begun. Since this study we have ceased to give vitamin K routinely to our premature infants.

The only mineral that needs to be administered is iron. The premature infant suffers a reduction of hemoglobin until about ten weeks of age, regardless of birth weight. We estimate the child's hemoglobin and erythrocytes beginning at the third week of life; if the decrease is below 10 gm. of hemoglobin, we administer iron. If it falls below 9 gm. of hemoglobin, we give a transfusion and then iron. About 50 per cent will need iron therapy. The simple U.S.P. iron and ammonium citrate is as good a preparation as any. This is given in 50 per cent solution, one or two drops to each feeding. We were not able to demonstrate that vitamin B_{12} had any marked hematonic effect.

Transfusions and Oxygen Therapy

A word may be said here about transfusions and oxygen therapy in premature infants. Szewczyk[24] has recently advised against excessive oxygen concentrations and advises minimal amounts as a prophylaxis against retrolental fibroplasia. The delay of transfusions until the retinal vascular tree has returned to normal has also been advocated. From 1942 to 1947 we cared for 101 premature infants under 1500 gm., 6 per cent of whom suffered from retrolental fibroplasia. From 1948 to 1953 we cared for 519 premature infants under 2500 gm., 120 of whom, or 22 per cent, were under 1500 gm. There were no instances of retrolental fibroplasia in any of these infants.

There was no change in the care of these babies during the nine year period. All were fed a mixture of lactic acid milk and breast milk, except those under 1500 gm. and those having feeding difficulties, who were fed pure breast milk. All were given 40 per cent oxygen for forty-eight hours after birth, and all under 1500 gm. were given continuous 40 per cent oxygen from birth until they had regained this weight. The average amount of oxygen for those under 1500 gm. was 5000 cubic feet per baby. All our premature infants are given blood transfusions if their hemo-

globin falls below 10 gm. or their red cells below 3,000,000. It can, therefore, be seen that we give plenty of oxygen and many transfusions to our premature infants. The only difference in care that might account for the lower incidence of retrolental fibroplasia in our premature group is that we give breast milk as a feeding. Whether this contains some protective substance we do not know.

Prevention of Infection

The final cause of premature mortality is infections. Because of their natural susceptibility and their prolonged hospital stay, premature infants are particularly prone to infections. Perhaps the greatest advance in the care of premature infants in the last decade is the recognition that premature care requires isolation and protection from the rest of the hospital, and a medical and nursing staff trained in the care of the premature.

Infections are difficult to diagnose in the premature infant, since there are no characteristic physical signs. Jaundice will occur in about half of all infectious conditions. The same is true in laboratory tests; about one half will show anemia, and a white blood cell count over 12,000. It is best to remember that if the premature infant fails to gain, vomits or has diarrhea, it may have an infection. For this reason some clinics give antibiotics routinely to all premature infants. Clifford[5] states that from 1948 to 1952 the mortality fell from 50 to 34 per cent in 508 premature infants, and of those dying under one week of age from 32 to 8 per cent. In their program prophylactic administration of aqueous penicillin, 50,000 units intramuscularly, is given every six to eight hours for seven to ten days, and sodium sulfadiazine, 20 to 30 mg. per kilogram of body weight, per twenty-four hours intramuscularly. This procedure was carried out in all infants over three days of age, and to all at any age whose history or examination caused them even to suspect contact with infection or possible injury or abnormality.

It has not been our policy to administer antibiotics prophylactically, but all premature infants that show any sign of infection, or have been exposed to such, or that fail to gain weight, vomit or have diarrhea, are given pure breast milk and 100,000 units of depository penicillin daily, and streptomycin, 0.1 gm. per kilogram of body weight, until a definite organism is found. Then the antibiotic may be changed to suit the individual organism.

SUMMARY

These are the principal causes of premature mortality. What seem to have been significant trends have been indicated. It is with pleasure that

those who have been working with the premature infant note the increased attention that has been given them by all physicians. This interest in the early life of these little people can only indicate that a more hopeful outlook for this period will surely follow.

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BLOOD OXYGEN STUDIES IN THE PREMATURE

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The clinical opinion and observation that premature infants do less well if obstetrical delivery is performed under general analgesia and anesthesia is well established and documented.[1,2,6,10] Masters and Ross[6] at Washington University in St. Louis had the unusual opportunity to observe the premature infant mortality rate in a large series of patients delivered where caudal and spinal anesthesia were used. These were compared to a parallel series in the same institution where general anesthesia, no anesthesia, maternal analgesia, and pudendal block anesthesia were used in the delivery of prematures. In the caudal anesthesia and spinal group no analgesic drugs were given to the mothers. The results of this study proved that caudal and spinal anesthesia were twice as safe for the premature infants as when other methods were used. The uncorrected premature fetal mortality in the conduction anesthesia group was 10.7 per cent as compared to 20.8 per cent in the other group.

The main contributions obstetricians have been able to make toward the reduction of premature infant mortality have been in withholding depressing drugs from the mother while she is in premature labor and the use of conduction types of anesthesia for the patient in premature labor.

There were those who tended to believe that maternal anesthesia or analgesia had but little effect on the respirations of the newborn, full term or premature infant, if excessive amounts of morphine, Demerol, barbiturates or inhalation anesthesia were not used. Experience and statistics were quoted by advocates of both schools of thought.

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ANESTHESIA OR ANALGESIA IN RELATION TO BLOOD OXYGEN SATURATION

In order to prove to ourselves and to others the importance of no analgesia or no general anesthesia in improving premature infant survival, we undertook a series of experiments.[9,10] The first series of experiments were performed on full term normal infants immediately after birth and for several hours after delivery.[9]

Oxygen saturation studies were done on the capillary blood of ninety-four full term newborn infants. The infants were born vaginally by normal spontaneous or outlet forceps delivery after various forms of maternal anesthesia. Capillary blood samples were drawn at birth, one-half hour, and one hour after birth. In some cases samples were collected two, three, twelve and eighteen hours after delivery. The anesthetics studied were regional, ether with or without neonatal supplemental oxygen, nitrous oxide, cyclopropane, and Pentothal sodium, all carefully administered for short periods (ten to twelve minutes at the termination of the second stage of labor). Significant differences were found when regional anesthesia was compared with the whole group of general anesthetics with respect to percentage of infants whose one-hour oxygen saturation was above 90 per cent. Any oxygen saturation above 90 per cent was considered normal.

In the regional anesthesia group 45 per cent of the infants were 90 per cent oxygen saturated or over at one hour of life. In the ether anesthesia series three hours of life were necessary before a similar number of the infants reached 90 per cent oxygen saturation.

Artificial resuscitation, which was given if respirations were not spontaneously established within three minutes after birth, was required for none of thirty infants born of mothers receiving regional anesthesia. One of ten infants from the Pentothal sodium series; three of ten after nitrous oxide; fourteen, or 45 per cent, of thirty-one infants from the ether series; and seven, or 54 per cent, of infants born of mothers receiving cyclopropane anesthesia required artificial resuscitation.

Our conclusions were that a significantly higher percentage of the infants reached oxygen saturations above 90 per cent at one hour when regional anesthesia was used than when general anesthesia was used. No full term infants were damaged by any of the anesthetics in the amounts used, but had the infants been premature even this small amount of anesthesia might have been injurious. It was felt that, since relatively small amounts of general anesthesia depressed the early attainment of adult levels of blood oxygenation in these healthy full term infants, premature infants might be expected to react in at least the same degree of adversity.

Through the work of Eastman,[3] Smith[7,8] and ourselves[9] we were familiar with the pattern of blood oxygen saturation in the normal full term newborn. The normal term infant exists in the uterus at a blood

oxygen saturation level of 50 per cent. The full term normal infant, if untraumatized and not depressed by drugs that have entered its circulation through the placenta, will within a matter of fifteen to thirty minutes after delivery have made adjustments to its new worldly environment that permit 90 to 95 per cent oxygen saturation of its blood.

Anesthesia or Analgesia in Premature Infants

Similar studies on the ability of premature infants to attain normal adult levels of blood oxygen saturation in the early neonatal period had

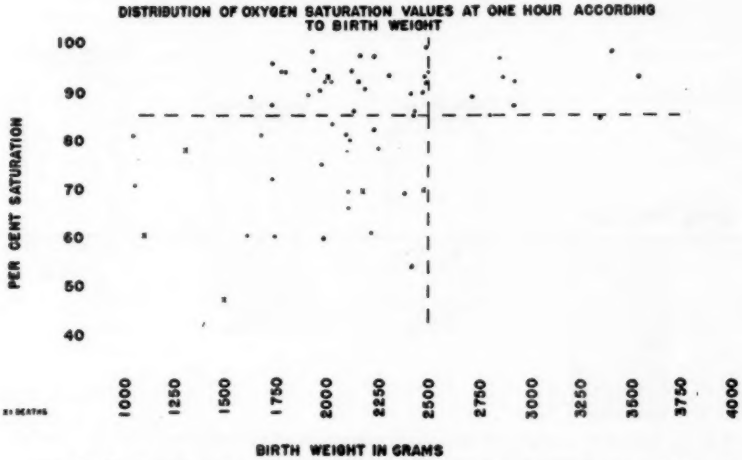

Fig. 11. Each of the above infants was placed in an incubator, the atmosphere of which was 50 to 60 per cent saturated with oxygen. The infants were in the incubator from soon after birth until at least one hour had passed. (Taylor, Scott and Govan: Am. J. Obst. & Gynec., Vol. 62.)

not been performed. We undertook a study to measure this particular physiologic aspect of respiration.[10] The results of this study are shown on Figures 11 and 12. A study of the data reveals that the premature infant is less able to oxygenate his blood in a 50 to 60 per cent oxygen atmosphere during the first hour of life than the full term infant. Forewarned by our previous experiments and clinical studies on the effects of maternal analgesia in small amounts on the oxygen saturation of normal, healthy full term infants, we felt that the giving of maternal anesthesia and analgesia in premature labor would depress even further the physiologic depression of the premature newborn's ability to properly oxygenate his blood during the early hours of life.

Figure 11 suggests that the degree of blood oxygen saturation at one

hour of life may be directly proportional to birth weight. The number of premature infants in the lower weight groups, however, was insufficient for final conclusion.

The reduced ability of the immature infant to oxygenate its blood embraces several other observable facts. The irregular respirations and shallow breathing are probably a manifestation of immature cerebral respiratory control and receptivity. Poor musculature of the thorax and diaphragm is present in all but the most vigorous premature child.

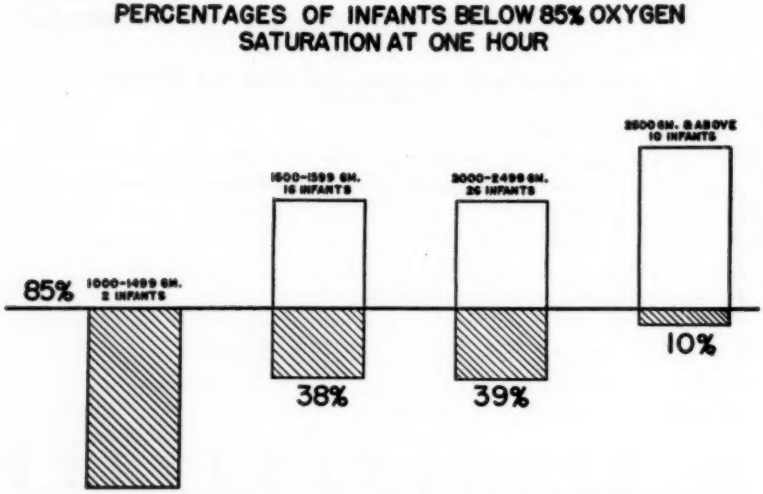

Fig. 12. Effect of prematurity on oxygen saturation of the newborn's blood. (Taylor, Scott and Govan: Am. J. Obst. & Gynec., Vol. 62.)

Comparative studies of capillary development in the medulla of full term and premature infants have been published by Mali and Raiha.[5] They have shown in a striking manner the degree of anatomic immaturity of the capillaries of the medulla in the premature as compared to the full term infant. The immature structure might be expected to be accompanied by immature respiratory function.

Klemola[4] performed similar studies that show the relative degrees of pulmonary tissue immaturity in premature infants as compared to full term infants.

The premature infant has measurable anatomic and physiologic inadequacies that must be compensated for by improved obstetrics. Since premature infants have a physiologic disability in making the early neonatal adjustment from 50 per cent oxygen saturation to 90 per cent or more oxygen saturation, this disability should not be further depressed by drugs given to the mother.

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ANEMIA IN PREMATURE INFANTS

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Anemia is listed among the numerous physiologic handicaps of the premature infant.[23] Interest has been revived in recent years in more accurately assessing the problem of anemia in premature infants. It is our purpose to discuss this problem from the standpoint of significance, etiology and management.

GNEERAL CONSIDERATIONS

Investigators differ in their opinion as to what degree of anemia constitutes a handicap in premature infants. On the basis of present knowledge it is impossible to answer this important question. To do so will necessitate correlation of oxygen needs with oxygen supply at the tissue cell level, and a consideration of the many variables affecting oxygen transport and release. These variables include cardiac output, volume of circulating erythrocyte mass, total body hemoglobin, efficiency of enzyme systems concerned with oxygen metabolism, variations in biochemical and physical properties of hemoglobin, variations in the structure of erythrocytes, and efficiency of oxygenation of hemoglobin by the pulmonary system.

Although considerable research is being done along these lines, our knowledge of the significance of anemia in premature infants is by no means complete, and one is obliged to depend upon routine hematologic studies for evaluations.

Serial determinations during the first two to three months of life reveal a rapid reduction of hemoglobin concentration and erythrocyte

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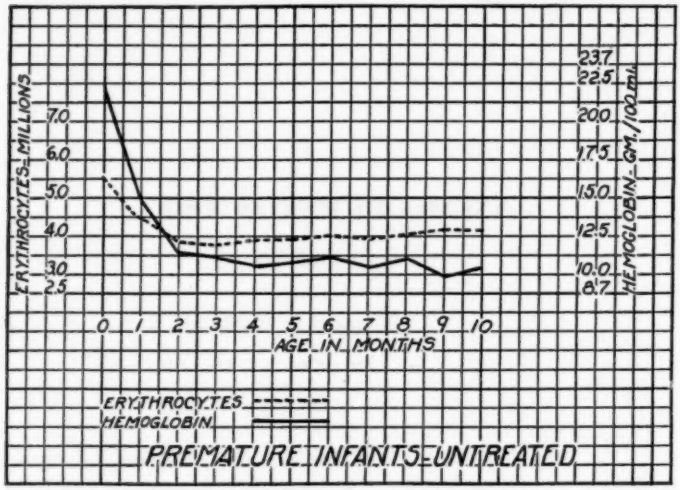

Fig. 13. Erythrocyte count and hemoglobin concentration in premature infants. (From Brenneman's Practice of Pediatrics, original data of Merritt and Davidson.[25] Reprinted with permission of W. F. Prior and Company, Inc.)

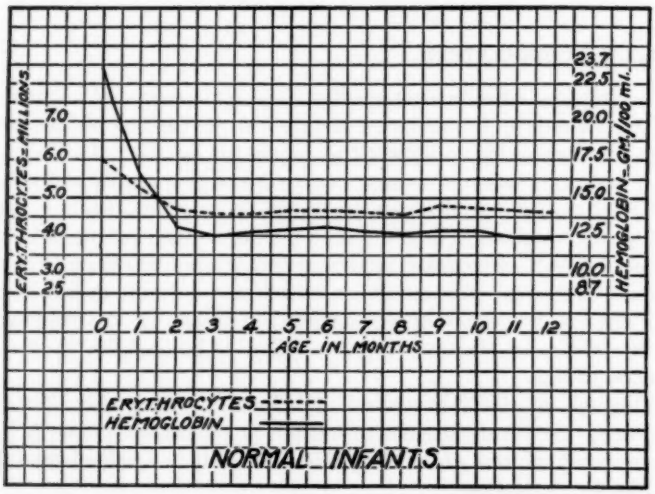

Fig. 14. Erythrocyte count and hemoglobin concentration in normal infants. (From Brennemann's Practice of Pediatrics, original data of Merritt and Davidson.[25] Reprinted with permission of W. F. Prior and Company, Inc.)

count in premature infants to levels below those usually found in full term infants of the same postnatal age (Figs. 13 and 14). Various investigators have reported different findings concerning rate of occurrence and degree of anemia which develops during the first few months (Table 6). In all probability these discrepancies may be attributed to the nutritional status of the mothers, as well as to slight differences in the degree of prematurity in the groups observed. Also the reported rate of

TABLE 6. *Anemia of Prematures Observed by Various Authors*

AGE OF INFANTS	BIRTH WEIGHT	GESTATION	HEMOGLOBIN		ERYTHROCYTES IN MILLIONS PER C.MM.	AUTHOR
			PER CENT	GM. PER 100 ML.		
10 weeks	—	—	—	6.5	—	Findlay[10]
10 weeks	—	6–7 months	55	—	3.2	Abt and Nagel[1]
12 weeks	—	8 months	63	—	3.8	
—	—	—	50	—	3.0	Lucas and Washburn[24]
20 weeks	1–1.5 kg.	—	—	6.55	—	Reedy and others[32]
1 year	1.5–2.5 kg.	—	—	9.0	—	
1 year	—	—	—	11.0	3.8	Merritt and Davidson[25]
12 weeks	Under 2½ pounds	—	—	—	2.8	Diamond[3]
	2½–3½ pounds	—	—	—	3.2	
	3½–5 pounds	—	—	—	3.5	
7 weeks	—	—	—	9.2	—	Mitchell and others[26]
8 weeks	—	—	—	7.7	3.0	Tuttle and Etteldorf[41]

return toward values comparable to those of normal full term infants of similar ages varies according to different observers.

Cooley,[5] in his analysis of the data from several sources, emphasizes the similarity between the course of the anemia of prematurity and that observed in full term infants and feels that ordinarily the anemia which develops in the premature infant is the result of an accentuation of the same processes operating in the development of physiologic anemia in the full term infant. He states: "These curves of hemoglobin and red cell averages have a general contour very much alike, with a rapid fall in hemoglobin from the polycythemic state at birth, beginning during the second week and reaching a low level at from 2 to 3 months. There is a slight peak at about 6 months, and then a practically level line until the end of the second year, at which time there is a slow rise to the adult normal which is reached during adolescence." He emphasizes differences

in the degree of anemia when premature and full term infants are compared.

The differences between the physiologic anemia of full term and premature infants have been reproduced graphically from the data of Merritt and Davidson[25] and are shown in Figures 13 and 14. Practically all investigators and writers have emphasized the direct proportionality which exists between the degree of prematurity and the severity of the anemia. Based on this concept, the anemia in premature infants may be classified as either (1) physiologic or (2) pathologic. The latter may be the result of an accentuation, or prolongation, of physiologic anemia; or it may be attributable to a variety of causes not associated with the normal physiology of these infants, i.e., hemolytic disease, hemorrhage, infection, and so forth.

The erythrocyte count and hemoglobin concentration, at any time, depend upon the simultaneous operation of the following processes: (1) hemoglobin synthesis and erythrocyte formation, (2) erythrocyte destruction and hemoglobin degradation, and (3) relation of rate of growth to hematopoiesis.

We shall now consider the factors which influence these processes in the genesis and therapy of the two types of anemias.

PHYSIOLOGIC ANEMIA

Rate of Hemoglobin Synthesis and Erythrocyte Formation

It has been generally accepted that a significant reduction in hemoglobin synthesis and erythrocyte formation occurs during the first few weeks of life of prematurely born infants. Recent studies by Schulman and Smith,[38] using measurements of circulating erythrocyte mass and total body hemoglobin, have borne out this thesis. After this initial lag in hematopoietic activity there occurs a resumption of hemoglobin synthesis sufficient to maintain a constant hemoglobin concentration at a time when there is progressive weight gain. At the age of fourteen to sixteen weeks it appears that the premature infant has regained the total body hemoglobin with which he was born. Although the total hemoglobin has reached birth levels at this time and the blood volume has fallen from 110 to 75 ml. per kilogram, the concentration of hemoglobin (grams per 100 ml.) in peripheral blood is considerably decreased when compared to birth levels and to full term infants of similar age (Figs. 13 and 14).

The processes of hemoglobin synthesis and erythrocyte formation are modified by the following:

Transition from an Environment of Low Oxygen Tension to One of High Oxygen Tension at the Time of Birth. Polycythemia and high hemoglobin levels present during intrauterine life are attributed to the

relatively low oxygen tension in the maternal placental circulation. With increased environmental oxygen tension at the time of birth and the onset of respiration, the need for accelerated activity and erythropoietic centers no longer exists, and the bone marrow becomes relatively less active.

It is interesting that erythrocytes of premature, and to a somewhat less extent full term, infants contain predominantly the fetal type of hemoglobin. This is advanageous to the fetus during intrauterine life in making oxygen more readily available at the tissue level,[34] but it is believed to be insignificant in influencing the rate of either formation or destruction of erythrocytes.[38]

Immature Bone Marrow. During early intrauterine life the fetus depends primarily upon extramedullary centers for synthesis of hemoglobin and production of erythrocytes. During the last trimester of pregnancy the bone marrow assumes a rapidly increasing responsibility in these functions. Therefore it is apparent that an infant born prematurely is equipped with a relatively hypoactive bone marrow at a time when extramedullary hematopoiesis is diminishing. It is significant that erythrocytes formed in extramedullary centers enter the circulation at an earlier stage of development and have a shorter life span than those derived from the bone marrow.[12,17,31,34]

Iron Stores. Ordinarily, adequate stores of iron are available for stimulation of bone marrow and normal synthesis of hemoglobin. This iron is derived from maternal sources and from hemolyzed erythrocytes in the infant.[37] Because of destruction of erythrocytes in premature and full term infants during the first few weeks of life, anemia attributable to inadequate stores of iron during this period is unlikely.[38] However, by comparing iron-treated with nontreated prematures,[25,32,41] it has been observed that iron therapy is effective, at least to some degree, at a time when iron derived from hemolysis of erythrocytes would be expected to be adequate.

Other Factors. Various antianemic substances other than iron, namely, copper, molybdenum and cobalt, vitamins C and B_{12}, pteroylglutamic acid and amino acids, are required for maximal hemoglobin formation.[4,12,15,18,20,23,39] The role of these substances in the genesis of physiologic anemia of premature infants has not been completely assessed, and specific deficiencies in premature infants have not been demonstrated.

Rate of Erythrocytic Destruction and Hemoglobin Degradation

Erythrocytes of the newborn infant are apparently more susceptible to mechanical trauma[21] and to hemolysis by hypotonic sodium chloride solutions[6,11,23,27,40,42,44] than erythrocytes of older children and adults.

It has also been shown that erythrocytes of premature infants exhibit an increased susceptibility to hemolysis by hydrogen peroxide when compared to erythrocytes of adults.[16] The data of Schulman,[38] obtained by determining total erythrocyte mass, indicate that the erythrocyte population in the premature infant has a shortened life span. The greater incidence of physiologic jaundice in the premature infant has been attributed in part to a decreased life span of circulating erythrocytes in these infants.[20]

Reasons for altered resistance to hemolysis have not been satisfactorily clarified, and the phenomenon is demonstrable only during the first few days of life. Kaplan[22] has apparently demonstrated that erythrocytes of full term infants do not have increased mechanical fragility and that cord blood erythrocytes from full term infants have a normal survival time. For these reasons it cannot be stated accurately to what degree the anemia of premature infants is influenced by these factors. It would appear, however, that increased destruction of erythrocytes plays at least a minor role.

Relation of Rate of Growth to Hematopoiesis

The daily weight gain, expressed in grams, is less in premature infants than in full term infants, and is less in smaller than in larger premature infants.[14] When weight gain is related to birth weight, however, it is observed during the first year of life that the smaller premature infants usually gain more rapidly (per cent of birth weight) than larger ones or full term infants.[5, 10, 20, 26] Thus during a time of relatively rapid increase in body size the infant's total body hemoglobin is decreasing and until the age of fourteen to sixteen weeks is less than the amount present at birth.[38] Utilizing values from the literature for blood volume,[38] hemoglobin concentration[8, 25, 41] and weights at birth and at six weeks of age, it may be calculated that the hemoglobin in grams per kilogram of body weight in the premature infant, although similar to that in full term infants at birth, is approximately 60 per cent of that of the latter at age six weeks.

Prophylaxis and Therapy

Summarizing briefly the usual trends in hemoglobin concentration and erythrocyte count in premature infants during the first year of life, the following facts deserve re-emphasis. During the first two or three months both hemoglobin concentration and erythrocyte count are reduced from the polycythemic levels present at birth to levels somewhat lower than those found in full term infants of comparable postnatal ages. After this there is a leveling off of both values and a gradual return toward values for normal infants.

There is no direct evidence that deficient iron storage is a factor in the initial reduction of hemoglobin concentration, and the question as to whether or not iron should be administered during the first weeks of life remains a disputed one. Some investigators[3, 23, 29, 35, 38] advocate delaying iron therapy until the second or third month of life on the thesis that the bone marrow will not respond to iron therapy during the period of physiologic anemia, and others[32, 41, 45] have presented evidence that the early administration of iron is more effective in ameliorating the anemia than therapy which is delayed until later. The data of Schulman[38] indicate that anemia cannot be explained on the basis of depleted iron stores until after the age of fourteen to sixteen weeks. Wolff,[45] however, has postulated that medicinal iron may be more readily available for hemoglobin synthesis than stored iron, a fact which, if true, would explain the benefits observed following early iron therapy. Ability to excrete administered iron is extremely limited,[37] and iron therapy during a "nondeficient" period may result in the storage of at least a part of administered iron for future use. Undesirable effects of excessive iron storage in tissues have been emphasized[37, 38] and must be considered in evaluating dosages of this element. Iron is readily absorbed by the premature infant;[30] since no deleterious effects and some benefits have been associated with the administration of small doses of this element during the early neonatal period in premature infants, we recommend its early use.

There is no doubt of the value of medicinal iron after the second and third months of life. Studies on iron absorption indicate that ferrous iron is more readily absorbed than the corresponding ferric salts[17, 28] and that the absorption of iron is adversely influenced by high phosphorus : iron ratios.[2, 19] The utilization of iron is influenced by copper, molybdenum, cobalt and vitamin C.[9, 18, 29, 39] The use of these substances in the care of premature infants has not been adequately evaluated.

The authors recommend molybdenized ferrous sulfate in daily doses which supply the equivalent of 90 mg. of ferrous sulfate (20 mg. of elemental iron), principally because it is well tolerated. Diamond[29] recommends ferrous sulfate at three months of age in doses of 1 to 4 grains daily. In recent studies Reedy and co-workers[32] have used iron and ammonium citrate in combinations with liver extract and copper early in daily dosage supplying 390 mg. of iron and ammonium citrate (60 mg. of elemental iron).

Iron preparations must not be administered with foods if maximum absorption is to be expected. It is also advisable to give dilute preparations in order to avoid gastrointestinal upsets.

Blood transfusions are neither indicated nor recommended to correct physiologic anemia except as an emergency procedure.[3] No permanent benefit is derived, and spontaneous resumption of bone marrow activity is probably delayed.[38]

PATHOLOGIC ANEMIA

On our premature infant service we consider any of the following to be indicative of pathologic anemia: (1) hemoglobin concentration of 13 gm. per 100 ml. or less at the time of birth, (2) abnormally rapid rate of reduction in hemoglobin concentration in the first months, (3) hemoglobin concentration less than 8 gm. per 100 ml. at any time, and (4) unusual persistence of low hemoglobin concentrations associated with physiologic anemia. It must be remembered that pathologic anemia may result from the same factors that produce physiologic anemia. This is particularly true with reference to iron stores when the mother is anemic, or in cases of twin or multiple births. The effects of the latter factors become manifest usually after the infant has reached two or three months of age.

Since anemia due to these causes is frequently of the iron deficiency type, early administration of iron as outlined earlier is generally indicated and usually beneficial.

If premature delivery is expected, measures should be taken to minimize the degree of anemia. These include the following: (1) administration of vitamin K in doses of 5 to 20 mg. to the mother at the onset of premature labor; (2) permitting the cord to cease pulsating before it is clamped; (3) affording good care of the premature infant in order to decrease the possibility of infection; and (4) minimizing hypoxia.

In addition, certain diseases discussed below, not peculiar to the premature infant, may produce pathologic anemia.

Hemolytic Anemias

Erythroblastosis fetalis due to Rh or ABO incompatibility is proportionally more severe when it occurs in premature infants, particularly males.[8] The serious manifestations of this disease, such as anemia, hyperbilirubinemia, edema and hepatosplenomegaly, appear early and are directly related to the degree of prematurity.

According to Diamond,[8] prematurity itself is an indication for exchange transfusion when evidence of erythroblastosis is present. This procedure, however, is more formidable in this group of infants. ACTH in doses of 25 mg. daily, in four divided doses at six hour intervals, appears to influence favorably the course of erythroblastosis fetalis.[13, 33]

One of the most serious conditions causing hemolytic anemia is *sepsis neonatorum*. This may occur in utero as a result of maternal sepsis, endometritis or premature rupture of the membranes. Neonatal sepsis may result from infection through abraded skin or mucous membranes, circumcision wound, umbilical stump, and respiratory, digestive and genitourinary systems.

The incidence of neonatal sepsis is directly related to the quality of

premature care. It must be remembered that signs of severe infection, such as leukocytosis and fever, may not be present in cases of overwhelming infection in full term and particularly in premature infants. Once the condition is suspected, the offending organism should be identified and sensitivity to various antibacterial agents determined. It is our practice to administer penicillin, streptomycin and other broad-spectrum antibiotics as soon as blood culture and culture of appropriate specimens have been obtained. Continued use of broad-spectrum antibiotics is accompanied by danger of hypoprothrombinemia; administration of vitamin K is advised during such periods of treatment. In these cases the severity of anemia and the shocklike state imposed by an overwhelming infection frequently necessitate blood transfusions.

Hereditary hemolytic anemias (hereditary spherocytosis, sickle cell anemia, thalassemia) rarely become manifest during the first year of life, and only in rare instances are they encountered in premature infants.

Excessive hemolysis due to drugs, mismatched blood transfusions, or toxins are likewise rare in the premature infant.

Cytomegalic inclusion disease, a recently described generalized disease characterized by cytoplasmic inclusions, hemorrhagic tendency, thrombocytopenia, jaundice and anemia, should be considered among the causes of anemia during the first three months. Clinical and laboratory findings may simulate those of erythroblastosis. This disease carries a high mortality rate, and the etiology has not been determined. No definitive therapy is known.

In hemolytic anemias, iron which is released and stored is available for synthesis of hemoglobin. Therefore iron therapy would not appear to be indicated; nevertheless it has been observed to be beneficial in certain instances, especially following infection. If the hemolytic process is sufficiently severe, blood transfusions may be necessary to re-establish adequate oxygen-carrying capacity.

Blood Loss

Included in this group are those conditions which result in postnatal blood loss and those in which the usual quantity of blood is not delivered to the baby from the placenta during labor and delivery.

Loss of blood from the fetal side of the placental circulation may be severe and require emergency treatment. This may occur (1) in cases of abnormal insertion of the cord, (2) as a result of trauma to the cord during delivery, and (3) in cases of abnormal implantation when surgical section of the placenta is necessary for delivery. Another important factor resulting in a considerable decrease in the quantity of blood delivered to the infant from the placenta is injudicious clamping of the umbilical cord. It has been shown that approximately 100 ml.[43] of blood

may enter the infant's circulation after delivery if the cord is not ligated until it ceases to pulsate. In premature infants this becomes especially significant and constitutes a relatively high percentage of total blood volume. Furthermore, the iron contained in this additional amount of blood will be made available through the processes of hemolysis for re-use in future synthesis of hemoglobin. Therefore, when a premature infant is delivered, the cord should not be ligated until it ceases to pulsate unless (1) requirements for resuscitation necessitate ligation and severance, or (2) congenital hemolytic anemia is suspected. In the latter event the cord should be ligated immediately in order to decrease the number of maternal Rh antibodies that enter the baby's circulation.

The premature infant is especially susceptible to conditions causing hemorrhage. The clotting mechanism is less efficient, blood vessels are more fragile, and there is a greater predisposition to hypoxia. Specifically, hemorrhage may be associated with (1) hypoprothrombinemia (hemorrhagic disease of the newborn, hepatitis, and so on), (2) rupture of blood vessels during birth (tentorial tears, visceral bleeding, massive cephalhematoma or extensive ecchymoses) and, rarely, (3) such events as bleeding from a duodenal ulcer, Meckel's diverticulum, intestinal polyps, reduplication of the intestine, and the like.

In discussing the role of vitamin K in preventing hemorrhagic disease of the newborn, Gordon[15] and Dam and co-workers[7] cite a number of controversial reports concerning the benefits of (1) administration of this vitamin to the mother prenatally and (2) to the newborn infant. They conclude that vitamin K should be given to all premature infants because of an increased incidence of spontaneous hemorrhages in this group. Dam[7] found hypoprothrombinemia during the first days of life, which could be prevented by administration of vitamin K to the mother or infant. They also report low prothrombin levels at the time of birth in cases of intrauterine asphyxia. We routinely administer 1 mg. of vitamin K intramuscularly every twelve hours for three doses to premature infants.

There is some disagreement among different authors as to the quality and quantity of platelets in the premature infant at the time of birth.[20, 25, 34] However, thrombocytopenic and nonthrombocytopenic purpuras, secondary to infections or drugs, may cause blood loss in premature infants to the same degree as in full term infants. Hemorrhage due to thrombocytopenia associated with malignancies such as leukemia, although rare, occasionally occurs, and produces anemia which is superimposed upon that already present in the premature infant.

According to Hess,[20] the premature infant probably requires the same amount of vitamin C as the full term infant. However, it has been demonstrated[15] that the stores of this vitamin are less than those of the full

term infant. Consequently, it may be assumed that vitamin C deficiency resulting in hemorrhage is relatively more frequent in the premature infant. The role of vitamin C in hematopoiesis has been mentioned previously. The administration of ascorbic acid, 25 to 50 mg. daily, should be instituted during the first week of life.

The only effective treatment for severe anemia resulting from blood loss, regardless of the cause, is transfusion. In milder cases iron therapy is indicated and will aid in the recovery.

Bone Marrow Hypofunction

As mentioned previously, physiologic anemia of premature infants is due, at least in part, to a functional immaturity of the bone marrow. Accentuation of this hypoactivity may be associated with a variety of causes resulting in a more severe anemia. As in children of any age, infection, to which the premature is especially susceptible, is of great importance and is the most frequent cause of anemia in infants and children. Toxic depression of bone marrow may also occur as a result of drugs or overexposure to x-ray irradiation. Metastatic tumors, especially neuroblastoma and primary malignancies of blood-forming tissue, may cause profound anemia by invasion of the reticuloendothelial system. These become increasingly important as the infant matures.

Conditions such as achondroplasia, osteogenesis imperfecta, familial aplastic anemia with multiple congenital defects (Fanconi's syndrome) and congenital hypoplastic anemia associated with an inborn error in erythropoiesis are associated with anemia and may be significant early in life.

Recently Smith[36] has reviewed certain "ill defined" anemias with common hematologic features suggesting impaired cell formation which are not attributed to deficiencies of antianemic factors or infiltrations in the bone marrow. This group of anemias includes those attributed to hypoplasia and hypofunction of the bone marrow occurring during infancy and childhood. The syndrome of "nonhemolytic anemia of the newborn" is described and associated with the aregenerative phase of erythropoiesis characteristic of the newborn infant. Although the anemia of premature infants is not specifically discussed, conditions are mentioned that would apply to the premature as well as the full term infant. Smith has emphasized the suppressive effects of blood transfusions in hypoplastic-aplastic anemia.

For normal bone marrow function to proceed, it is presupposed that the known factors necessary for hemoglobin synthesis and erythrocyte formation and maturation must be supplied by a diet adequate in minerals, proteins and vitamins. In severe cases of hypoplastic anemia not

reponding to adequate intake of these factors, or to therapeutic trials of substances such as iron, pteroylglutamic acids, vitamin B_{12}, and so forth, transfusions may constitute a last resort.

SUMMARY

With our present knowledge it is difficult to assess the significance of anemia in the premature infant. On the basis of hemoglobin concentration and erythrocyte count, this anemia may be classified as physiologic or pathologic.

Physiologic anemia in premature infants is similar to that in full term infants, but is present to a greater degree and is proportional to the degree of prematurity. The anemia is attributable to (1) transition from an environment of low oxygen tension to one of high tension, (2) increased fragility of erythrocytes and (3) hypofunction of bone marrow. Iron store appears to be adequate during the first two or three months of life; however, iron therapy begun soon after birth ameliorates physiologic anemia. After two or three months of age it is generally agreed that iron therapy is beneficial. Blood transfusions are not indicated in the treatment of physiologic anemia unless emergency states arise, in which case the anemia may be classified as pathologic.

Pathologic anemia may be attributed to an accentuation of degree or duration of physiologic anemia. This may be noted in cases of anemia in the mother during pregnancy or in cases of twin or multiple births. A variety of pathologic conditions not peculiar to the premature infant may be responsible for this type of anemia. These include conditions which cause increased destruction of erythrocytes, depression of bone marrow, or usual blood loss. Blood transfusions are frequently necessary in the treatment of anemia due to increased erythrocyte destruction or to unusual blood loss. Iron therapy is frequently beneficial in the latter, less beneficial in the former.

Hypofunction of the bone marrow more rarely results in anemia, but may occur in all degrees from mild with temporary depression to severe with aplasia. Transfusions in the former are to be discouraged.

Pathologic anemias can, for the most part, be prevented through proper antenatal and premature care.

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RETROLENTAL FIBRO-PLASIA

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Retrolental fibroplasia is one of the terminal stages of a disease frequently affecting the eyes of premature babies, and rarely of full term infants. It is today probably the most common cause of blindness in the preschool child. Its importance, however, is even greater than we have thus far appreciated. For every child who suffers total or partial blindness as a result of retrolental fibroplasia there is most likely one or more who has as a terminal stage of the same disease other ocular disturbances which become handicaps in life. These disturbances include partial or extensive destruction of the retina by fibrosis, pigmentary degeneration, and myopia.

HYPOXIC RETINOPATHY AND ITS SEQUEL (RETROLENTAL FIBROPLASIA)

The initial ocular changes which may terminate with the development of retrolental fibroplasia are first appreciated either immediately after birth or after the first week of life. Rarely are they seen beginning during the first six days of life if at birth the eyes were normal. Because these changes may terminate with not only retrolental fibroplasia, but also other permanent ocular changes, because initially they appear to be limited to the retina, and because there is sufficient evidence to show that they are produced by interference with oxygenation, I shall refer to them by the term "hypoxic retinopathy."

Hypoxic retinopathy may be of sudden or gradual onset and may range in severity from extremely mild to severe. It is characterized initially by edema of the peripheral retina, vasodilatation with or without hemorrhages, tortuosity of the retinal vessels, and neovascularization. Mild

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changes may consist entirely in edema of the peripheral retina with mild or moderate vasodilatation with or without neovascularization. Severe cases may show marked and extensive retinal edema, marked vasodilatation, tortuosity and neovascularization, and hemorrhages which may invade the vitreous.

As the disease progresses, depending on its severity and on the stage at which regression takes place or not, various lesions are produced. In its most severe form all the ocular tissues are involved either primarily or secondarily. The retina becomes totally detached, the vitreous invaded by fibrous tissue, and as a result an opaque mass forms behind the lens. The iris becomes atrophic and adherent to the lens, which itself may develop opacities. The anterior chamber may become extremely shallow or nonexistent. The cornea may become opaque. The globe itself may shrink; during secondary glaucoma, which is a frequent complication, it may occasionally enlarge.

In the other terminal forms there may be no involvement of the anterior segment except the formation of a total or partial retrolental mass consisting of atrophic retina and fibrous tissue. Milder cases may terminate with the formation of retinal folds or elevated or flat peripheral masses of opaque tissue. Occasionally, the only residua are clumping of pigment—areas resembling chorioretinitis or glial tissue proliferation.

The least severe residual of hypoxic retinopathy is myopia, which may range from mild to very severe. The myopia is frequently unequal and complicated by astigmatism. The fundi may be normal in appearance, but not infrequently there are vitreous opacities, granularity of the pigment, and mild or gross distortion of the disk.

ETIOLOGY

Though there are still many who dispute the relationship of oxygen to retrolental fibroplasia, the evidence in support of this is most impressive. Lesions resembling retrolental fibroplasia have been produced experimentally in animals by exposing them to reduced oxygen tensions, by acclimatization to high oxygen tensions and sudden withdrawal, and supposedly by prolonged exposure to high concentrations of oxygen. Some have reported that retrolental fibroplasia appears when oxygen is used indiscriminately and tends to decrease in incidence when the use of oxygen is restricted. Others have noted the appearance of this disease when supplemental oxygen is terminated suddenly, and a reversal of the disease when oxygen is administered in high concentrations.

In my experience with over 800 premature babies, hypoxia produced by the improper use of oxygen, by diseases or by conditions producing hypoxia has been the only cause of retrolental fibroplasia at the Christian Welfare Hospital in East St. Louis, Illinois.

Some of the observations we have made are as follows:

Hypoxic retinopathy tends to appear most frequently in babies kept in high concentrations of oxygen for over six days.

It is most severe and most frequent in babies kept in high but varying concentrations of oxygen for prolonged periods of time.

It is much less frequent and less severe in babies who receive oxygen in low concentrations.

It occurs in a very mild form or not at all in babies receiving oxygen for less than six days after birth (provided the eyes were normal at birth, and there is no complicating disease).

It rarely occurs in babies who do not require and who receive no supplemental oxygen after birth.

The first signs of hypoxic retinopathy are usually noted after supplemental oxygen has been terminated or suddenly reduced either intentionally or accidentally (as, for example, by an accidentally disconnected oxygen tubing).

The disease can be induced in babies acclimatized to high amounts of oxygen by sudden withdrawal from oxygen or rapid reduction in available oxygen.

The early changes can be made to regress by restoring an infant to an atmosphere of high oxygen concentration.

The early changes can be prevented from appearing in an infant acclimatized to a high concentration of oxygen by gradual weaning to a normal atmosphere.

The disease either in its mild or severe form is present in some babies immediately after birth.

It occasionally makes its appearance during acute respiratory infections or anemias.

It occasionally appears two or more times in a single infant.

The second or third attack of this disease is usually much more severe than the preceding one, and often so fulminating that the changes become irreversible in a short time.

Together with Dr. William Knaus we have found that transfusions after hypoxic retinopathy has developed invariably make the disease much worse, but that repeated transfusions while an infant is in a high concentration of oxygen with normal fundi allow for rapid and even sudden transfer of the child to a normal atmosphere.

These and other observations lead one to the following conclusions:

1. Retrolental fibroplasia is one of the terminal stages of retinal hypoxia—a hypoxia produced most frequently by acclimatizing an infant to an oxygen-enriched atmosphere and too rapid withdrawal.

2. The severity of this disease is dependent on (*a*) the degree and duration of the hypoxia, and (*b*) the sensitivity of the retina to hypoxia—

a condition determined by previous exposure and compensation to hypoxia and one most frequently caused by great variations of oxygen concentrations in incubators or a hypoxic insult at birth.

3. Retrolental fibroplasia is almost completely preventable by proper attention to hypoxia.

Let us further develop this theory and investigate its implications and ramifications.

Oxygen Requirements of Retina

In the premature baby the tissue which probably has the highest oxygen utilization and requirement is the retina, because it is a highly specialized neural tissue in a very active stage of development. At the time of birth or shortly prior to it, it is perfectly possible that the infant can be subjected to a decreased oxygen intake sufficiently severe that the requirements of the retina are not met. This can be caused by a difficult, prolonged labor, oversedation, as twilight sleep or anesthesia, some placental anomaly, or the like. If this decrease in oxygen is sufficiently severe or prolonged, the retina will show some pathologic response. This response consists in retinal edema and vasodilatation with or without leakage of serum or blood. This response can be mild if the oxygen deficiency is slight or extremely severe if the deficiency is great. In my study I have noted that many premature babies after birth show retinal edema and vasodilatation. A few show these changes plus retinal hemorrhages and vitreous exudation, and occasionally a child is born with definite retinal detachment and gross hemorrhages.

Likewise, there are many premature babies born who undergo no hypoxic episodes and have normal-appearing fundi at birth.

We have then, at birth, two distinct types of babies: those who have undergone no experiences with hypoxia, and those who have been traumatized by hypoxia. The one has a normal retinovascular tree; the other a vascular system which has been damaged to the extent that blood or serum was able to escape through its walls.

In Normal Infants. We shall first follow the course of the child who has not been injured by hypoxia and who is not given supplemental oxygen after birth. This child had a relatively low oxygen saturation and a relatively great red blood cell count in utero. He was blue, but certainly not hypoxic. Immediately after birth he begins to breathe and turns pink. His blood is now saturated with oxygen far in excess of what he has been acclimatized to and far in excess of his actual requirements. Over a period of time what we call physiologic anemia develops, which may well be a response to the presence of more oxygen than the baby actually requires. This anemia is of gradual onset and produces no sudden change in the

amount of oxygen available to the baby. As such a child grows he is at no time subjected to hypoxia. If, however, he should have a sufficiently severe respiratory infection or a disease producing a sudden anemia, or if he should be transferred to a rarefied atmosphere, it is quite possible that the quantity of oxygen in his blood stream may fall to the point at which the retina is not satisfied. If this should happen, compensatory dilatation of the retinal blood vessels would take place. And since these vessels have always been normal, they would not allow leakage of blood or serum unless the hypoxia were so severe that the increased blood flow was insufficient to satisfy the retina with oxygen.

I have yet to see a child who had normal fundi at birth, who was not given supplemental oxygen, and who had a progressive type of hypoxic retinopathy even during respiratory infections. Over 300 such babies varying from 2 to 5 pounds in weight have been studied.

In Hypoxic Infants. The course of the child who has been injured by hypoxia at birth, but is not given supplemental oxygen, is somewhat different. Because the oxygen saturation in a newborn rises considerably above what it was in utero, more oxygen than the retina actually requires is now carried to it. Depending on how severe the hypoxic insult was, there is a rapid or slow regression of the changes of hypoxic retinopathy. Retinal edema subsides, the vessels return to normal size, and petechial hemorrhages disappear, usually in one to three days. More severe changes are slower in regression. Gross hemorrhages, for example, may persist for many days, and the retina anterior to them may remain edematous until they are absorbed. Fortunately, I have never seen a case with these changes which did not regress after birth; but certainly there must occur cases with hypoxic changes incurred prior to or at birth so severe that they are irreversible.

Such a child, if his development is not complicated by upper respiratory infections or diseases interfering with oxygenation, will also not have a second attack of hypoxic retinopathy. If such a child should, however, have a disease (as an upper respiratory infection) or condition which would cause the oxygen in his blood stream to drop below the requirements of the retina, his retinal vascular tree would also respond to the local hypoxia by dilatation. Since, however, this vascular tree is not normal, but was previously traumatized by hypoxia, it reacts in an abnormal way. The dilatation becomes out of proportion to the stimulus, and leakage of serum and blood frequently takes place. Fortunately, this response regresses as the child's illness improves, but if the illness is severe or sufficiently prolonged, it is quite likely that the retinopathy may progress to the point at which it becomes irreversible. In my experience, though I have seen several babies with hypoxic retinopathy at birth and a recurrence of the disease during respiratory infections or severe anemia, in

only two was the recurrent retinopathy so severe that prolonged treatment with supplemental oxygen was decided upon. Both regressed and except for myopia have normal-appearing eyes.

We can now safely predict that babies who have normal fundi at birth and never require supplemental oxygen will not suffer hypoxic retinopathy, and that babies with hypoxic retinopathy at birth of mild or moderate severity will regress spontaneously and are not liable to have this disease again if they are not given supplemental oxygen.

In Hypoxic Infants with Oxygen Administration. Now we can turn our attention to those babies who require supplemental oxygen after birth. Babies who are administered oxygen even in high concentrations for short periods of time after birth or during periods of cyanosis are not liable to hypoxic retinopathy even on sudden transfer to a normal atmosphere, because exposure to an enriched atmosphere has to be of sufficient duration for acclimatization to take place. In my experience premature babies can be kept in high concentrations of oxygen for five to six days and removed suddenly without any or with only slight funduscopic changes, provided they do not have a respiratory infection or a recent anemia, and provided they did not have a severe hypoxic retinopathy at birth.

Let us now follow the course of babies kept in a moderately or highly enriched oxygen atmosphere for a sufficient length of time to become acclimatized to it. If the oxygen concentration has been constant, if no disease or condition has developed which could cause hypoxia, the fundi of both the babies who had reversible hypoxic retinopathy at birth and those who were normal at birth will apparently be alike. On sudden transfer, however, to a normal atmosphere, a remarkable change takes place, usually within twenty-four to forty-eight hours. The children with the healthy vascular tree may show mild or moderate vascular engorgement, none or slight neovascularization in the periphery of the fundus and some peripheral retinal edema. The others, however, having a hyperreactive vascular system, will show much more vasodilatation, more severe retinal edema, neovascularization, and frequently hemorrhages and exudation into the vitreous. Over a period of days the funduscopic picture in the first group may regress, that in the second gradually grow worse.

If now these children are replaced into the same concentration of oxygen within one to three days after their hypoxic insult, another remarkable phenomenon takes place. Usually, in one to three days vascular engorgement, tortuosity, neovascularization and edema regress; the regression is more rapid in the children who had no hypoxic retinopathy at birth. After several days there may again be no difference in the funduscopic picture of either group of babies. Should these children be again subjected to a sudden transfer to a normal atmosphere, the response in the fundus is much more violent, more abrupt in onset (recognizable

sometimes in a matter of hours), frequently characterized by retinal and vitreous hemorrhages and more severe in the twice previously traumatized babies. What is more significant is that restoration to the same oxygen concentration may be in some cases insufficient to bring about regression, and frequently significantly higher concentrations have to be used. If these babies have been acclimatized to very high concentrations of oxygen and if the hypoxic response has been severe, reversal of hypoxic retinopathy may be impossible.

It is not necessary that a child be withdrawn from supplemental oxygen for these changes to appear. In transferring a child from an enriched to a normal atmosphere we are not withdrawing him from oxygen, but merely reducing the amount available to him in inspired air. Similar and equally severe changes can be brought about by reducing the amount of supplemental oxygen—as, for example, when we subject a child to a drop from an 80 per cent oxygen atmosphere to one of 40 per cent. Nor is it apparently always necessary for visible funduscopic changes to appear in order to make a child hyperreactive to oxygen changes.

Respiratory infections and diseases producing a sudden anemia may produce the same effects as sudden withdrawal from oxygen.

It is obviously unwise to acclimatize a child to an abnormal atmosphere and then place him suddenly or too rapidly in a normal atmosphere. There are two physiologic methods of approach to the problem of acclimatization. We can either so gradually reduce the concentration of oxygen available that the oxygen-carrying apparatus and metabolism adjust slowly to decreased oxygen; or we can increase the oxygen-carrying capacity of a child by transfusions immediately prior to transfer into a normal atmosphere. Through repeated transfusions to anemic babies acclimatized to high oxygen (60 or more per cent for one or several weeks) Dr. William Knaus has been able to prevent the development of hypoxic retinopathy when these babies were suddenly transferred into a normal atmosphere. Most babies showed little or no recognizable funduscopic changes on sudden withdrawal; a few showed minor changes which regressed spontaneously.

Though it is logical to suppose that giving transfusions to a child after hypoxic retinopathy has developed would tend to improve the condition, in practice it usually makes the condition much worse. It is probable that the vascular walls are in such a weakened condition that any increase in blood volume or pressure increases the amount of vascular leakage and that the extravasated serum and blood act as barriers for proper oxygen absorption by the tissue which requires it. We have noted severe intraocular hemorrhages following transfusions to children with hypoxic retinopathy on several occasions.

The most satisfactory method for returning a baby to a normal atmosphere is through gradual reduction of the concentration of oxygen over

a prolonged period of time. Regardless of whether the baby had been sensitized to hypoxia by an insult at birth, if the available oxygen is reduced slowly enough, if no severe anemia or respiratory embarrassment develops to complicate the picture, hypoxic retinopathy does not develop. The length of the weaning time will of course depend on the degree of the initial oxygen concentration and on whether the retinovascular tree had been previously traumatized.

We can conclude, then, that babies may be kept in an oxygen-enriched atmosphere for prolonged periods of time; that they will not have hypoxic retinopathy, provided the oxygen concentration is kept constant and they do not have a severe anemia or respiratory embarrassment; that they will have hypoxic retinopathy if they are transferred suddenly to a significantly poorer oxygen atmosphere than that to which they are acclimatized; and that gradual reduction of supplemental oxygen till atmospheric levels are reached protects them from relative hypoxia.

Unfortunately, whenever a child is placed in a high concentration of oxygen for a long time, he is in danger not only of becoming acclimatized to an abnormal atmosphere, but of developing a hyperreactive vascular tree due to significant changes in the oxygen concentration in his incubator. It is exceedingly difficult to maintain a constant high concentration in an incubator for long periods. Mechanical defects or inadequacies added to human failures are so frequent that one must almost presuppose that many if not most children kept in a high concentration of oxygen for a long time have been subjected to one or more significantly severe variations in the oxygen available to them and that their retinovascular tree has been sensitized to hypoxia.

MAINTENANCE OF OXYGEN REQUIREMENTS OF PREMATURE INFANTS

Few people realize the difficulties in maintaining a constant oxygen concentration in a small closed box such as an incubator. If, for example, it is desired to keep the concentration at 80 per cent in an incubator and the oxygen is flowing at 8 liters per minute, slightly less than 3 liters of air have to be diffusing into the incubator at the same time. This small flow of air reaches the incubator through the vents or seams of the incubator. Control of this diffusing air is exceedingly difficult, because in most incubators it is determined not only by the area of the openings and leaks to the incubator, but also by the temperature difference between the incubator and the nursery and the air currents in the nursery. Whenever the temperature in the nursery tends to approach that of the incubator, the concentration of oxygen in the incubator will rise. Whenever the temperature of the nursery drops significantly, the oxygen concentration in the incubator will also drop. In some incubators this

variation is not severe, but unfortunately in the most frequently used incubators this variation is at times tremendous.

Even under the most ideal conditions, such as can exist in an air-conditioned nursery where there is little or no variation in temperature or air currents, any child in an incubator can be subjected to large variations in oxygen concentrations.

Oxygen to an incubator is supplied by individual tanks, by a battery of tanks or from a piped system. If oxygen comes from a large source—as, for instance, a battery of tanks—unless a sensitive pressure regulator is part of the system, variations in the pressure can so affect the usual oxygen flow valves that large variations in oxygen flow will take place. A slight fall in pressure will cause a fall in the liters of flow of oxygen, and the attending personnel will have to be continuously adjusting the liter flow valve.

If oxygen is supplied by individual tanks, the danger of variation in oxygen concentration is even greater. As the pressure in the tank falls, the liter flow valve will also reduce the amount of oxygen flowing into the incubator unless it is of a special type. But added to this is an even greater danger. In most hospitals because of the effort to reduce expenses, tanks are not changed until they are empty. Unless there is someone at constant attention, a tank can empty and a child remain without oxygen for varying periods of time. If, for example, a tank empties during feeding time or during an emergency in a premature nursery, the child may be without oxygen long enough to suffer severe damage. In some hospitals tanks are not changed except by maintenance men. If the nurse in charge is fortunate, she may get immediate service, but it is not unusual for long delays to occur between the time when an oxygen tank empties and a new one is delivered and attached to an incubator. It is always advisable to change an oxygen tank when it is low rather than when empty.

Flow valves are also a source of great variation in oxygen concentration. After a certain amount of usage the bushings tend to wear, so that the valve becomes erratic. If mounted in such position or such a level that attending personnel or the incubator can accidentally come into contact with them, it is not at all unusual for a worn valve to shut itself off and stop the flow of oxygen. Valves should be checked and adjusted periodically, and should always be mounted so that they are above the level of the incubator and out of the way of the nurses or aids.

A common method for adding moisture to the incubator is by bubbling the oxygen through water held in a large jar. The jar itself is attached by a screw top to a lid with the oxygen intake and outlet tubes attached to it. If this jar is not properly tightened, if it has a defect in its rim, or if the rubber gasket has not been fitted properly, a large quantity of oxygen will leak out into the nursery rather than into the incubator.

This kind of accident is not rare and is usually not discovered until the oxygen concentration in the incubator is measured.

It seems superfluous to say that the oxygen tubing should be connected to the incubator and the source at all times. Yet unless the incubators are immovable and the tubing so placed that it never gets in the way of whoever attends to the incubator, the tubing will at times be accidentally disconnected from the incubator and may be on the floor for a considerable time before it is discovered.

Lids, portholes and adjustable vents are another source of great variation in oxygen concentration in incubators. Lids, unless perfectly tight, allow escape of the warm incubator air and cause an unpredictable dilution of the oxygen; furthermore, since in many incubators the lid is the only avenue of approach to a child, it is frequently opened for feeding, taking of temperatures, changing of diapers, and so on. As soon as the lid is opened, the heated incubator air escapes, and the incubator oxygen concentration drops to about that of room level. After it has been closed it takes several minutes for the concentration to rise to its previous level. Occasionally the lid itself may accidentally be left completely or partially open for varying lengths of time.

Portholes with tight-fitting sleeves through which the nurse or aid can insert her arms to attend the baby, although highly desirable features on an incubator, are also at times left open because the nurse or aid is distracted or careless.

The crude adjustable vents present on many incubators were no doubt intended to allow some control of air circulation in the incubator. This they do in the most gross, unpredictable way. Only under the most ideal conditions, when the nursery temperature and air currents are constant and the temperature in the incubator unvarying, can some control of the oxygen concentration be maintained by adjusting vents. In my experience adjustable vents have had only a nuisance value—being frequently left open when they should be closed.

It is impossible for one conscientious person to be held continuously responsible for proper administration of oxygen to a baby for prolonged periods of time. Because of our present working schedules (eight-hour day; five- or six-day week) a minimum of six persons have access to a particular baby's incubator and determine how well the oxygen will be administered. In hospitals where a baby is attended by whoever is available at the moment, the number of persons concerned is considerably higher. It is obvious that carelessness on only one attendant's part might adversely influence the oxygen concentration in any incubator and that the accidental interruptions or frequency of variations in oxygen concentration will to a great extent depend on the caliber and training of the attending personnel.

When all these factors are taken into consideration, it must be obvious that many babies will have hypoxic retinopathy while apparently in con-

tinuous high oxygen, that some will have the condition and improve, and that others will progress to the development of retrolental fibroplasia or related terminal conditions even while apparently receiving sufficient oxygen.

OXYGEN REDUCTION AND DEVELOPMENT OF HYPOXIC RETINOPATHY

Why does oxygen cause hypoxic retinopathy and eventually retrolental fibroplasia? The answer is that it does not do so, but that hypoxia is caused when the oxygen is suddenly withdrawn because the oxygen-carrying apparatus does not readjust quickly enough to the change in available oxygen.

Some observers, however, are of the opinion that it is solely the toxic effect of oxygen which brings about this disease. This school of thought, however, cannot account for several known facts. There are many premature babies who have all the classical early symptoms of this disease at birth even though they have not been exposed to supplemental oxygen, nor for a sufficient length of time to atmospheric oxygen. There are also babies who, having this condition at birth, show regression in atmospheric or supplemental oxygen and have it again weeks after birth under circumstances compatible with hypoxia and not with hyperoxia.

Early hypoxic retinopathy can be reversed by administration of concentrated oxygen (hyperoxia and not hypoxia).

Premature babies, in my experience, can be kept in high concentrations of oxygen for long periods of time and prevented from acquiring hypoxic retinopathy by gradual weaning. At our hospital, when an infant had hypoxic retinopathy while in a high concentration of oxygen, in every instance it was during an acute respiratory infection, a severe anemia or after the concentration of oxygen had been significantly lowered either intentionally or accidentally—but not while the concentration was high.

Yet the idea that overoxygenation is a factor in the production of this disease cannot be discarded. It has been shown that keeping animals in high concentrations of oxygen causes a shrinkage of the retinal vessels and inhibits the normal vascularization of the retina. It is within the realm of possibility that this inhibition, if prolonged and severe enough, produces hypoxia of the retina and so gives rise to the stimulus for the proliferation of abnormal blood vessels. This, however, in my opinion is unlikely.

It is most likely, however, that when an animal is kept in high concentrations of oxygen, the retinal vessels constrict and normal vascularization is inhibited, because the retina is supplied with more than sufficient oxygen for its metabolism. This vascular change may represent the method by which the retina acclimatizes itself to an overabundance of oxygen. As long as the same quantity of oxygen is available to the retina, no further change will take place. If the oxygen available is reduced, however

(as by an upper respiratory infection, severe anemia or a reduction in the supplemental oxygen), retinal hypoxia develops readily because of the paucity of retinal vessels. This hypoxia, if slight—as can be produced by gradual reduction in supplemental oxygen during the weaning period—presents just enough stimulus for slight dilatation and orderly vascularization. If severe, or if repeated on several occasions so that the vascular system becomes hyperreactive, abnormal neovascularization, vasodilatation, and the like, may take place; and once started, if severe enough, the chain reaction of tissue hypoxia, vasodilatation, neovascularization, stagnation, vascular leakage, increased tissue hypoxia, and so forth, takes place.

That the metabolism of the retina is also altered by being exposed to more than sufficient oxygen is also likely. Clinically, most cases of hypoxic retinopathy begin with retinal edema and vasodilatation (with or without exudation and hemorrhages). Occasionally, the most prominent initial symptom is a diffuse and profuse neovascularization. It is possible that the former changes are initiated by relative hypoxia of a retina habituated to high oxygen, and the latter by hypoxia caused by a reduction in circulating oxygen to a retina with an abnormally decreased vascular system. Both factors, however, may be of equal significance. But whether one or the other or both factors are involved, the stimulus for the vascular response is hypoxia, and the reaction to this hypoxia depends on the degree and duration of the hypoxia, and/or on the conditioned reactivity of the vascular system to hypoxia.

It is my belief that the cases of hypoxic retinopathy reported as occurring in babies while in high concentrations of oxygen (and experimental production of similar lesions in animals kept in high oxygen) represent instances of this disease produced by repeated hypoxic insults due to great variations in the concentration of the administered oxygen.

PREVENTION

It is useless to say that we must avoid premature deliveries if at all possible, since no obstetrician desires his patients to be delivered weeks before term. However, it is most desirable when a premature delivery is inevitable that the obstetrician not traumatize the baby by heavy sedation or anesthesia of the mother. The better the condition of the baby on delivery, the less likely is the danger of hypoxic retinopathy.

Administration and Concentration of Oxygen

1. Oxygen should not be administered to premature babies unless

there is definite indication that the baby requires it. The color of the baby is the best index. If the baby is pink, regardless of whether his respirations are regular or not, one can be sure that he is sufficiently well oxygenated and does not require supplemental oxygen.

2. If the baby's condition is such that it is apparent that he cannot survive without supplemental oxygen, he should be placed in a just sufficiently enriched atmosphere to maintain a good color. In other words, he should be given just sufficient supplemental oxygen to supply the deficiency which is present. What this minimum is depends entirely on the condition of the individual baby. Some require an atmosphere enriched to 30 per cent, others to 40, 50 or 60 per cent. If we keep in mind the fact that in utero a baby has a low saturation of oxygen and a high red blood cell count, that he is acclimatized to this relatively low quantity of oxygen, and that he does not immediately have a lower red blood cell count after birth, slight cyanosis should not alarm us and cause us to administer more oxygen than the baby actually requires.

3. Once it has been decided that a baby needs supplemental oxygen, every effort should be made to keep the concentration at the desired minimum. This, unfortunately, is no easy task.

To keep a concentration of oxygen stable one must first have a proper incubator. Lids, drop-down sides and crude, adjustable vents are objectionable features because they make it almost impossible to maintain constant concentrations of oxygen. Incubators so constructed that ventilation takes place only through a few predetermined unadjustable openings, that is, those which have no seams or lids which could leak, and are provided with portholes for attendance of the child, are highly desirable.

The oxygen inlet tube should be in such a position that the incoming oxygen is well diluted before it strikes the baby. In some incubators the inlet tube is placed within a few inches of the baby's head, so that simply by changing his position the baby is subjected to varying concentrations of oxygen. This is a most undesirable condition.

In an incubator whose ventilation is determined by a small, constant-speed circulating fan (such as in an Isolette incubator) the oxygen concentration can be controlled with reasonable accuracy by the oxygen liter flow valve. Since, however, to attain very low concentrations one must reduce the oxygen flow to well below 4 liters per minute, and since many valves are erratic when set to a flow of 1, 2 or 3 liters per minute, it is necessary that the valves be mechanically perfect and that they be checked frequently during operation. Furthermore, if the oxygen is piped from a large source, a sensitive pressure regulator should be part of the system. If the oxygen is supplied from individual tanks, the valve must be of a type uninfluenced by the pressure of the incoming oxygen.

Probably the safest way to govern the oxygen concentration within the

incubator is by diluting the pure oxygen with air in the desired concentration before it enters the incubator. This can be done with an adjustable Venturi type of valve. Though this is not an accurate way of providing high concentrations, it has proved satisfactory for maintaining moderate and low concentrations of oxygen in our incubators. The valve is attached through a hole drilled in the foot end of the incubator. The concentration is adjusted by a disk with various-sized openings which allow various quantities of air to be sucked into the incubator by the stream of flowing oxygen.

Regardless of the kind of incubator used and the precautions taken to insure a constant, unvarying supply of oxygen, there is only one way to determine the actual concentration. There is no alternative and no excuse for not measuring the concentration at frequent and regular intervals with a reliable oximeter, such as the Beckman oxygen analyzer (which we have found most satisfactory and dependable). The frequency with which these measurements have to be made depends entirely on the conditions in the nursery, the oxygen equipment available and the type of incubator. For example: oxygen concentration measurements at eight hour intervals are sufficient, provided the temperature in the nursery is thermostatically controlled so that it is constant, the oxygen supply is piped and its pressure constant, the flow valves are in perfect operating condition, the oxygen tubing is not routed through a humidifier, but connected directly and securely to the incubator, the incubator is of the Isolette type, and the attending personnel are well trained. The presence of any factor which might make it possible or probable that the amount of oxygen or air entering the incubator may vary makes it mandatory that measurements be made at much more frequent intervals.

4. If a child's condition is such that supplemental oxygen is required for one to five or six days, it is not necessary that he undergo a weaning into a normal atmosphere, provided he is not ill or anemic and has no persistent funduscopic changes from a hypoxic injury incurred at birth. A sufficiently severe anemia, if present, should be corrected by transfusions while the child is still in oxygen. He may then be suddenly transferred to a normal atmosphere. Severe upper respiratory infections may also contraindicate sudden withdrawal from oxygen unless the concentration has been low or exposure to it has not been prolonged. Fortunately, severe hypoxic retinopathy at birth is rare. If present, however, and if the child requires supplemental oxygen, it is probably best to keep such a child in a constant concentration till the changes regress and to wean him slowly to a normal atmosphere even though his general condition be such that prolonged oxygen administration would not be indicated.

5. Once a baby has become acclimatized to an enriched atmosphere—and this takes approximately one week—he should be weaned to a normal

atmosphere in slow stages. The weaning may be begun when it becomes apparent that the child can survive without supplemental oxygen, but again not in the presence of a respiratory infection, severe anemia or hypoxic retinopathy. Anemia should be corrected by transfusions before weaning is begun, but only if the fundi are normal. If a respiratory infection develops, the concentration should not be lowered till the child recovers. Hypoxic retinopathy may develop in a child while he is still in oxygen if he has been subjected to several sudden changes in the concentration of oxygen or if he has a severe respiratory infection. When the funduscopic changes are mild, the concentration should be kept constant till they regress before weaning is begun; when the changes are severe, the concentration should be raised considerably above its previous level.

Weaning of Infants from Oxygen

The method of weaning we have found most satisfactory is as follows: The concentration is dropped in increments of 20 per cent of the higher level at seven to ten day intervals. For example: if the initial concentration was 50 per cent, it would be dropped to 40 per cent. Seven to ten days later the concentration is reduced to 32 per cent, then 26 per cent, and finally to atmospheric pressure. Funduscopic examinations are made immediately prior to and two or three days after each lowering of the concentration. If there is more than the mildest type of funduscopic reaction, the weaning period is more prolonged.

It should be apparent that the lower the initial concentration, the less prolonged the weaning period. It should also be apparent that simply dropping the concentration by 10 or more per cent during each stage of the weaning period, while not significant in the high ranges, might be quite shocking to the babies when lower levels are reached. For example: A drop in oxygen concentration from 75 to 60 per cent represents approximately a 20 per cent decrease in the amount of available oxygen; whereas a drop from 35 to 20 per cent, though only a 15 per cent drop, represents a 40 per cent decrease in the available oxygen. This in some babies may precipitate a severe funduscopic response.

General Measures

1. Anemia must be combated before hypoxic retinopathy develops. It is a wise precaution to have frequent blood cell counts and hemoglobin determinations made on any infant whose general condition is such that prolonged oxygen administration becomes necessary to preserve life and to keep the red blood cell count high by repeated transfusions.
2. Respiratory infections should be treated promptly and energetically,

especially if they occur in babies acclimatized to an oxygen-enriched atmosphere. Antibiotics, proper humidity, frequent suction of the nasal passages, and decongestant nose drops are extremely important. Occasionally, what appears to be an upper respiratory infection proves to be an allergic response and will defy any usual treatment, but respond well to antihistaminics.

Failure to keep a premature baby's nasal passages free may result in the development of hypoxic retinopathy and progression to retrolental fibroplasia or one of the other terminal conditions in spite of administration of concentrated oxygen. This, I am told, is due to the fact that premature babies are poor "mouth breathers" and tend to become hypoxic whenever there is some nasal obstruction.

SUMMARY

Retrolental fibroplasia is one of the terminal stages of uncompensated retinal hypoxia.

Retinal hypoxia may be produced prenatally or at birth by diseases or conditions which produce a state of oxygen lack.

This type of hypoxic retinopathy usually reverses itself after birth because the blood oxygen saturation rises considerably above what it was in utero, but leaves the baby with a hyperreactive vascular system which will react abnormally when again subjected to hypoxia.

After birth retinal hypoxia is produced most frequently by habituating a child to an enriched atmosphere and by too sudden withdrawal. Severe respiratory infections or sudden severe anemia may produce the same effect.

The severity of hypoxic retinopathy depends on the degree, the duration of the hypoxia, and on whether the vascular system had been previously traumatized by hypoxia at birth, great variations in the oxygen available to him after birth, or respiratory infections or anemias.

To prevent retrolental fibroplasia and related conditions:

1. The obstetrician must not traumatize premature babies at delivery either physically or physiologically (twilight sleep, sedation and anesthesia).
2. Oxygen must not be administered to prematures unless they require it.
3. If oxygen is indicated, it must be used in minimal concentrations.
4. Every precaution must be taken to insure that the oxygen supplied be constant and unvarying in concentration.
5. Babies acclimatized to an enriched atmosphere must be weaned to a normal environment gradually.
6. Prompt and proper care should be given any significant anemia or respiratory infection.

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CONTINUOUS NEBULIZATION THERAPY:

A Technique for the Treatment of Abnormal Respiration in the Newborn Premature Infant

ROBERT DENTON, M.D.

Difficulties of respiration appear as the first item of a list of the "Physiologic Handicaps of the Premature Infant."[28] The inadequate anatomic and functional state of these infants is the basis for their predisposition to cyanotic attacks, delayed onset of spontaneous respiration, atelectasis and aspiration pneumonia. A recent report of a statistical analysis based on a large group of postmortem examinations of neonatal deaths[9] indicates that almost half of these cases were due to abnormal pulmonary ventilation. Frequently the complication of intracranial hemorrhage or asphyxia is added to the problem of inadequate pulmonary function. In many cases it is necessary to use mechanical means of resuscitation before spontaneous respiration is established. This discussion will not include methods of resuscitation of the premature infant and is limited to the after-care of respiratory difficulties.

In the past many premature infants were maintained in an incubator supplied with controlled heat and the addition of oxygen to the atmosphere. With increasing care in the performance of postmortem examinations of infants[9] evidence has been collected to show that many of these infants dying in the first forty-eight hours of life suffered from widespread obstruction of the peripheral respiratory tree. Recent developments in techniques of nebulization have undergone clinical trial for the relief of respiratory complications of the premature infant. Because the limited

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experience to date has shown considerable promise, this discussion will include a description of aerosol techniques, the theory of their effect on the problem of respiratory obstruction and the indications for use of aerosol therapy.

AEROSOL THERAPY: BACKGROUND AND TECHNIQUES

Aerosol therapy designates that branch of inhalation therapy in which a nebulizer (special type of atomizer) is used to add microscopic suspensions of liquids or solids in air or oxygen to the inhaled atmosphere. This technique has become firmly established in the therapeutic armamentarium for the treatment of several types of bronchopulmonary disease. Nebulization (aerosolization) of vasoconstrictor, bronchodilator and antimicrobial agents has been found practical in the management of severe obstructive disease of the respiratory tract.[3] The standard nebulizer is used to deliver small quantities of specific medicaments in the form of aerosol droplets for short periods of an intermittent schedule.

The term "mist therapy" has appeared in the recent literature[30] to describe a technique by which water in the form of a dense cloud, composed of microscopic droplets, is added to the atmosphere of an incubator or an oxygen tent. This atmosphere is maintained in a state of "supersaturation" by the technique of continuous nebulization.

Once spontaneous respiration has been established, after either resuscitative measures or a prolonged period of apnea, the equally serious problem of maintaining satisfactory ventilation and adequate oxygen and carbon dioxide exchange is of utmost concern. Routine incubator care includes a warm environment and an oxygen-rich atmosphere. The value of oxygen therapy is recognized as a supportive measure to increase the amount of circulating oxygen in the blood. It has been demonstrated[33] that an oxygen-rich atmosphere will sometimes change the irregular respiration of premature infants to a regular pattern.

Postmortem examinations of premature infants dying in the first forty-eight hours of life have revealed the presence of retained secretions in the finer divisions of the respiratory tree.[9] Microscopic sections have demonstrated a thin layer of these secretions plastered against the lining of the bronchioles, alveolar ducts and alveoli.[9,30] It is evident that air exchange will permit drying of this aspirated material over a short period of time. Progressive obstruction to respiration, i.e., gas exchange across the alveolar membrane, follows close upon this drying process. In addition, the drying and inspissation of this foreign material interfere with ciliary action of the respiratory mucosa which is responsible for continuous clearing of the entire respiratory tract.

Added to this mechanical factor causing widespread obstruction is the reaction of the mucous membranes to aspirated substances from the

birth canal. The secretion from the goblet cell is increased and is followed by inflammatory exudate. Edema of the lining membrane complicates the picture and further encroaches on the partially obstructed lumen of the tiny air passages.

Procedures such as tracheal intubation used during resuscitation may further complicate the problem of obstruction. Some trauma to the larynx is frequently unavoidable and may result in swelling of the glottic chink of the infant. Thus high obstruction may be an additional burden to the inadequate mechanisms of respiration in the premature infant.

The drying effect of oxygen has been studied[21] and has resulted in oxygen being labeled as an "antiexpectorant." The addition of moisture to an oxygen-rich atmosphere to combat this drying effect has received widespread application in recent years.

Several otolaryngologists[21,25] and pediatricians[5,28,30,31,35] recommend the use of high humidity in the atmosphere to maintain thin pulmonary secretions and reduce edema of the mucous membranes. Careful air conditioning is needed for those infants who require special climatic conditions.[10]

THEORY FOR CONTINUOUS NEBULIZATION

When the humidity supplied by an incubator is deficient, there is an increase of the transfer of moisture from the infant's mucous membranes to the tidal air. Loss of water from this large surface area leads to local drying and dehydration of the mucous lining of the entire bronchopulmonary system. With progression of this water loss the accumulation of thick, sticky secretion impedes normal function of the ciliated epithelium. Stasis and piling up of this material permit bronchiolar obstruction. Atelectasis, in addition to the original nonexpansion, follows progressive obstruction of the smaller segmental divisions of the bronchial tree. Aspiration of secretions, e.g., blood or mucus, from the birth canal further complicates this process. Infection is easily established in these nonaerated areas.

Some water loss takes place even if the tidal air taken into the infant's airway has been completely saturated with water vapor (100 per cent relative humidity) at incubator temperature. When air enters the respiratory tract, the temperature of this atmosphere is elevated to body temperature. As a result the original relative humidity decreases, and water is lost from the mucous membranes, although to a lesser degree. Therefore the inspired air-oxygen mixture will be more beneficial to the patient if it is completely saturated and also carries additional water in physical suspension. To overcome the loss of body water and to offset the serious sequelae of local dehydration of the respiratory secretions, the inspired atmosphere must carry this additional water, i.e., must be

supersaturated. This may be accomplished by suspending water in oxygen in the form of nebulized droplets. The microscopic size of these droplets (1 to 3 microns in diameter) permits their suspension in the form of a visible cloud or mist. In this way the saturation point is quickly reached, and the state of supersaturation desired can be steadily maintained. Additional therapeutic advantage is gained by using this nebulized mist as a vehicle for the deposition of specific medicaments upon the surface area of the respiratory tree.

APPARATUS AND TECHNIQUES

During the past five years several reports have appeared in the literature describing apparatus to accomplish continuous atomization[31,32,35] (large droplet size) or continuous nebulization.[3,5,26,32,37] The apparatus described have in common either the adaptation of a standard atomizer to generate a mist or a method of supplying a standard nebulizer with a source of fluid for prolonged nebulization. Recently several types of equipment have been made available commercially. Reference to hospital equipment houses will provide the source of a variety of devices to produce "cold fog."

Early experience with apparatus which utilized a standard glass or plastic nebulizer demonstrated the need for special attention directed to optimum standards to be met by equipment for this purpose. Continued experience demonstrated the need for special equipment of specific design to provide a standard aerosol for several clinical requirements.

1. The nebulizer should be designed to produce continuous large volumes of nebulized mist.
2. The volume of fluid nebulized per unit of time must cover all requirements for various cases, i.e., at least 1 cu. ml. per minute.
3. The aerosol produced must be composed of a limited droplet size.
4. Oxygen and fluid jets should be easily removable to permit rapid cleaning in the event of clogging.
5. The material used in fabrication must be nonreactive with all aerosol solutions and must stand up under hard use and heat sterilization.
6. Reliable performance must be assured without repeated adjustment or need for constant attention by attending personnel.
7. The apparatus should be easily and quickly portable to function in conjunction with all types of incubators, oxygen tents or similar enclosures.
8. The cost of such equipment should be within reasonable scale for hospital nursery use.

Because an instrument capable of supplying these requirements was not available at the time, the author secured assistance of technical engineering skill in an attempt to design and construct equipment for this

special purpose. Preliminary work, reported in 1951,[37] demonstrated the impossibility of successfully adapting a standard nebulizer to serve this special function. Subsequent developmental work produced an instrument* (Fig. 15) which has undergone extensive clinical application for

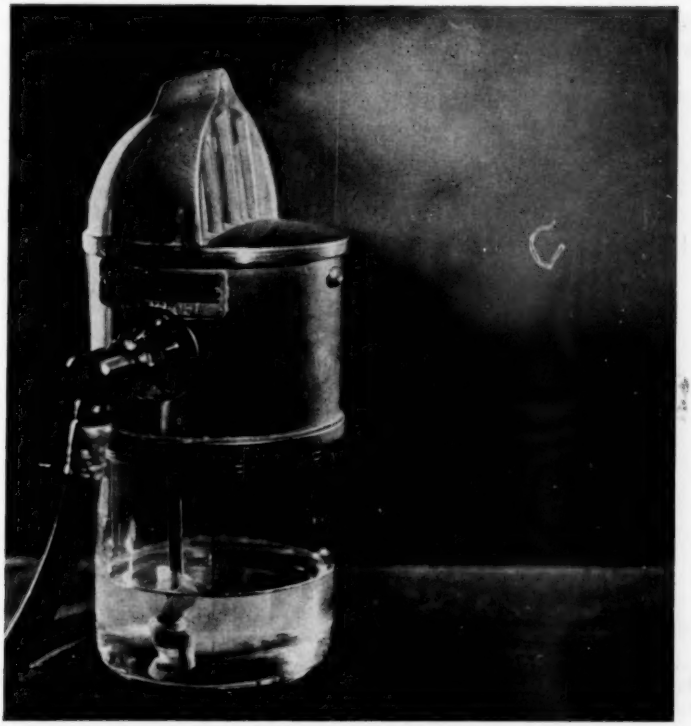

Fig. 15. Mist-O_2-Gen nebulizer during operation on an oxygen flow of 8 liters per minute. The self-feeding design, fabricated from cast aluminum and stainless steel, circulates fluid from the 380 c. ml. glass jar reservoir and nebulizes about 1 c. ml. per minute. Note the fluid feed tube fitted with a fine mesh nylon filter to prevent obstruction of the jets. The volume of fluid nebulized per minute exceeds that of standard nebulizers by 300 per cent. Eighty per cent of the droplets produced a range between 1 and 3 microns.[36]

the management of respiratory problems in the pediatric patient.[12] In a preliminary report[11] the special problem of the newborn infant was described to demonstrate the combination of continuous nebulization and incubator care. The nebulizer (known as the Mist-O_2-Gen) has been used in conjunction with several types of incubators in medical

* Available on physician's order from Mist-O_2-Gen Equipment Company, 2711 Adeline St., Oakland 7, Calif.

centers during the past three years. Pediatricians[14,30] and pediatric surgeons[17] have described the practical applications of this instrument to the care of the premature infant.

Although several types of nebulizers have been investigated, the great majority of our experience has been with the Mist-O_2-Gen instrument. The discussion to follow will therefore be concerned with the use of this nebulizer.

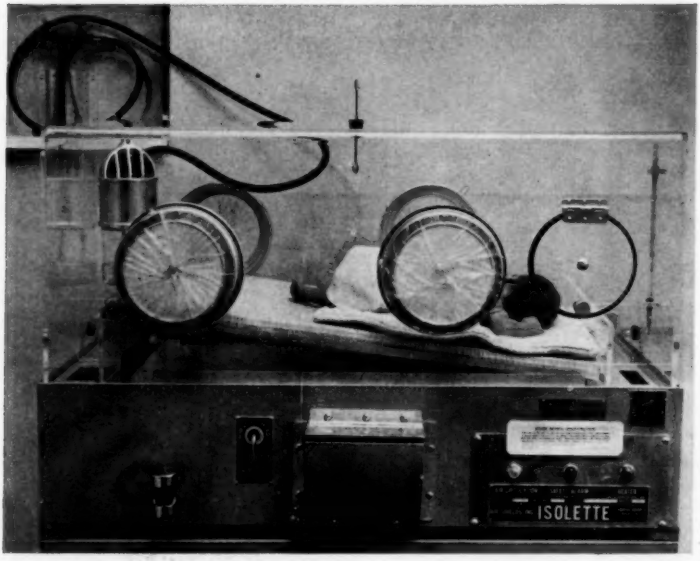

Fig. 16. Mist-O_2-Gen nebulizer installed in an Isolette incubator unit. Note the passage of the oxygen hose through one of 2 holes in the plastic wall, and the connection to the piped-in oxygen system.

When using the Mist-O_2-Gen nebulizer to adapt an incubator for continuous nebulization therapy, attention should be directed to the port of entry of the oxygen hose. In our experience the most efficient unit for incubator care is the Isolette,* which permits the oxygen hose to pass out of the enclosure through one of two holes in the back wall of the incubator (Fig. 16). The nebulizer is placed in one corner as illustrated. Another incubator in widespread use today is the Gordon Armstrong† unit (Fig. 17). When adapting this unit for use with the Mist-O_2-Gen nebulizer, the handle above the heating unit (Fig. 18) is replaced with a handle which encloses a port of the correct diameter to pass the oxygen hose and its end connector. In either case the hose is connected to a

* Manufactured by Air-Shields, Inc., Hatboro, Pa.

† Manufactured by the Gordon Armstrong Co., Inc., Cleveland, Ohio.

pressure type of flow-gauge* (Fig. 16) to assure optimum nebulization at the desired oxygen flows.

When treatment is needed, the incubator unit is brought to the prescribed temperature (80° to 85° F.), the nebulizer is installed as illustrated, and the oxygen flow-gauge is opened to 8 liters per minute. Saturation is reached within four minutes, as shown by a reading of 100 per

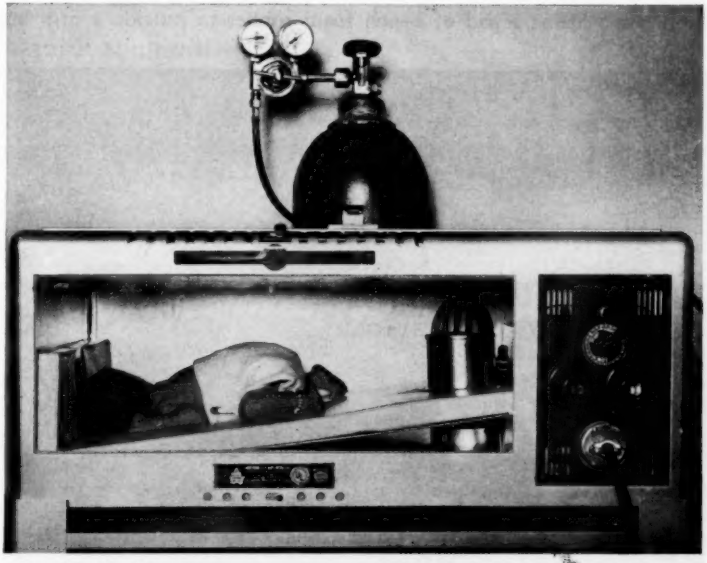

Fig. 17. Gordon Armstrong unit equipped with Mist-O_2-Gen nebulizer and postural drainage equipment. Oxygen hose enters the incubator through the replacement casting in the end handle. Note the plastic-covered foam rubber pads, and the location of the nebulizer in a cutout provided in the raised end of the inclined support. The Bourdon dial type of flow-gauge (illustrated) is always used for efficient operation.

cent relative humidity (Serdex Laboratory hygrometer). During the following few minutes nebulized mist collects in increasing density, maintaining an atmosphere of high oxygen tension supersaturated with moisture. The unit is now ready to receive the patient.

POSTURAL DRAINAGE

Although liquefaction of pulmonary secretions will take place within a brief interval, clearing of the air passages may be impeded because of deficient cough mechanism or ciliary action. To add the assistance of gravity, the prone position on an inclined plane of about 15 degrees

* The Bourdon dial type of flow-gauge is essential for proper operation of the Mist-O_2-Gen nebulizer.

from the horizontal has been used with satisfactory results.[2, 6, 13, 22, 23, 27, 30] Studies in the laboratory animal have demonstrated ciliary action to be twice as effective with the aid of gravity.[19]

The floor of the Isolette unit is equipped with an adjustable supporting pan to provide postural drainage. This advantage was obtained when using the Gordon Armstrong unit by using a postural drainage kit* designed to fit the interior of the unit (Fig. 17). Covering the sheet aluminum plate is a pad of 1-inch foam rubber to provide a firm but

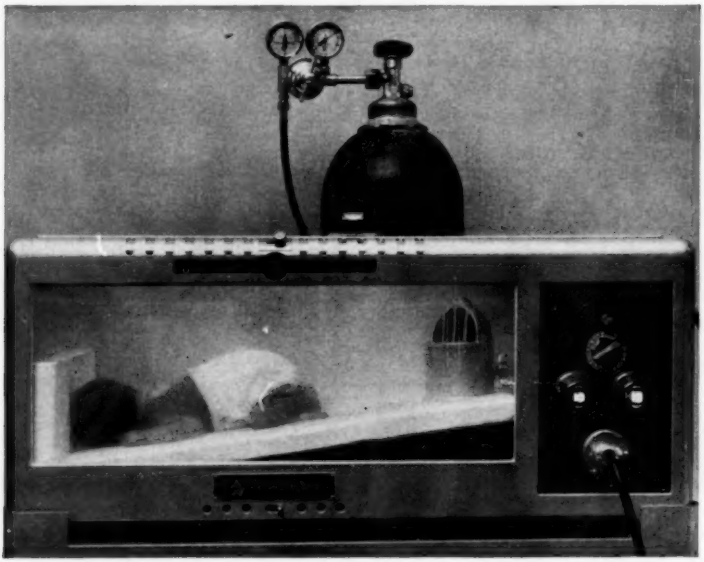

Fig. 18. Nebulized mist collected during a 4 minute period.

pliable surface. A second small pad of similar material stands in a vertical position (Fig. 17) at the end wall of the enclosure. Contact of the infant's head with the metal wall of the incubator is cushioned when the inevitable "sliding down" occurs. These foam rubber pads are enclosed in plastic covers to prevent absorption of water and to facilitate cleaning.

The prone position does not appear to impede respiratory exchange. Also, the infant does move and change position voluntarily. In this position the infant's nose and mouth, not the posterior pharynx, are in the most dependent position. Nursery attendants routinely observe secretions draining from the nose or the mouth in those cases in which aspiration or retained secretions have been evident. Even the weakest premature

* Mist-O_2-Gen Equipment Division of the Production Foundry Co., 2700 Magnolia St., Oakland, California.

infant tolerates the head-down position. The safety factor of adequate drainage from the tracheobronchial tree cannot be overemphasized. Maintenance of an open airway from the larynx to the smaller bronchi is of utmost importance to the relief of obstruction. A reliable suction apparatus and appropriate-sized two-hole catheters must be ready at all times to assist in clearing secretions from the upper respiratory tract. At times the procedure of tracheobronchial aspiration[4] may be indicated.

AEROSOL SOLUTIONS

The literature contains numerous papers describing the use of various agents delivered by intermittent aerosol therapy. Reports on clinical experience with techniques for cold humidification[5,31,35] comment on the use of distilled water to raise the relative humidity in oxygen tents or similar equipment. Experience during the past five years gained from both pediatric and adult patients treated with continuous nebulization has demonstrated the practical value to be gained from the use of special solutions for each individual case. Attention to the individual constituents of solutions is reflected in more prompt clinical response. No one prescription will serve to adequately manage all cases receiving continuous nebulization therapy. Agents have been selected from the field of intermittent aerosol therapy for their physical and pharmacologic effects.

To delay rapid evaporation of the aerosol droplets, glycerin is used in concentrations of 2 to 5 per cent. Glycerin alters the vapor pressure of water and thereby delays the evaporation of nebulized mist, permitting the droplets to reach the far recesses of the bronchopulmonary tree. This physical effect is clearly demonstrated by observing the cloud of nebulized mist produced before and after adding small quantities of glycerin to the water to be nebulized. The increased visibility and the prolonged duration of the mist are due to the effect of glycerin on each tiny droplet. Propylene glycol has similar effects when added to water solutions, but to a lesser degree. In addition, evidence has been reported[29] for the germicidal effect of this agent. Prolonged exposure of the bronchopulmonary tree to dilute concentrations of glycerin and propylene glycol is not harmful.

Bronchovasoconstrictors, Neosynephrine and ephedrine may be indicated to assist in reducing local edema of the mucous membranes. Effective concentrations, without untoward side effects, range from 0.05 to 0.1 per cent. These shrinking agents are used for limited periods of time, gauged by the clinical response.

Recent experience with wetting agents has shown an apparent increase in the speed with which gummy secretions are liquefied and mobilized. The rationale for the use of wetting agents is based on two

factors which appear to be active in these obstructive problems in the premature infant. Not infrequently obstruction of the bronchopulmonary tree is due to aspirated foreign material (mucus, blood, amniotic fluid or vernix). This material forms a dense film lining the peripheral passages. The desired liquefaction may be enhanced by the action of a wetting agent. Detergents (wetting agents) in aqueous solution have the obvious advantages of detergency: emulsifying properties and reduced surface tension.[8] The emulsifying properties assist in breaking up deposits of thick secretions.

Initial nonexpansion or atelectasis secondary to block and resorption frequently persists after gross obstruction has been relieved. Local deposition of wetting agents will reduce surface tension in the interface between mucous membranes in contact. This factor of cohesion of moist surfaces of the air passages has been pointed out[38] as the main force resisting aeration of atelectatic lung tissue. Evidence of this "sticking of moist surfaces" is described in the report by Berglund and Eder,[4] who used positive pressure and performed thoracotomy to expand atelectasis in premature infants. Objective proof of the importance of surface tension and evidence for the effect of "surface-active substances" on cohesive forces is presented in the report by Gruenwald.[18]

Microscopic examination of the lungs of premature infants who die in the neonatal period frequently reveals the presence of hyaline (vernix or asphyxial) membranes lining the respiratory bronchioles, alveolar ducts or alveoli. Evidence is presented[7, 30] which indicates that these membranes are composed of concentrated protein material. Their role in the production of abnormal ventilation has undergone extensive investigation.[30] The emulsifying properties of wetting agents assist in loosening purulent exudates of high protein content. It is reasonable to assume that the continuous deposition of a wetting agent on the surface of these membranes assists in their elimination by emulsification and the restoration of normal drainage mechanisms.

In addition to the purely physical effects on liquefaction of aspirated material and cohesion of moist surfaces, wetting agents potentiate the antibiotic effect of penicillin and streptomycin. Pulmonary infection frequently follows and may be superimposed on the obstructive factor. Although several detergents have undergone clinical and laboratory investigation,[15] the agent of choice at present is a nonionic substance (alkylaryl polyether alcohol) known as Triton WR-1339. Satisfactory results have followed the use of concentrations of 0.025 to 0.125 per cent.

In selected cases of infection superimposed on obstruction, soluble crystalline penicillin (500,000 units per 100 c. ml.) and streptomycin (0.5 gm. per 100 c. ml.) have been used. Systemic administration of antibiotics may also be indicated.

INFLUENCE OF A SUPERSATURATED ATMOSPHERE ON FLUID BALANCE

During the period of respiratory distress of the premature infant the support of fluid balance and prevention of dehydration are of utmost importance. All physicians who have encountered this problem have experienced the difficulties and danger of secondary aspiration of gastric contents when oral or gavage feedings have been started. Technical difficulties associated with parenteral fluid therapy in the tiny premature infant complicate the care of this emergency situation. The minimum of handling and disturbance during the period of abnormal ventilation is desirable.

Early in our experience with continuous nebulization therapy, after development of the Mist-O_2-Gen instrument had assured heavy concentrations of mist, we were impressed by the absence of the classical signs of dehydration usually seen by the fourth or fifth day. Although no fluids were given by any route, the attending nurses reported normal urination. In the face of the anticipated weight loss from catabolism of body tissues, we have observed either normal hydration or only "slight dryness" in these infants over periods as long as ten days.

Reports from investigators[7] have demonstrated the ability of the fetal lung to absorb water. The rich capillary network surrounding the alveolar structure presents a large surface for absorption. The lack of clinical signs of early dehydration may be reasonably explained by the introduction of water across the alveolar-capillary membrane.

INDICATIONS FOR THE USE OF CONTINUOUS NEBULIZATION THERAPY

The question of indications for the use of continuous nebulization therapy was proposed at a recent meeting of physicians brought together for the purpose of furthering knowledge of hyaline membrane disease.[30] At this meeting Gellis[30] advocated starting mist therapy immediately for "any infant with any difficulty during labor, including all infants born by cesarean section. If there is no respiratory distress during the first twenty-four hours, the infant can be removed from 'mist therapy' since the danger of developing hyaline membranes will be over."

DISCUSSION

Any therapeutic technique is as effective as the knowledge of those directing its use. Investigation of therapeutic failures in the field of inhalation therapy frequently reveals a total lack of knowledge on the part of the attending physician of the limitations or basic principles of the technique applied. Adequate care of equipment for nebulization therapy is essential to continued satisfactory performance. Proper attention to the

preparation of specific prescriptions for aerosol solutions is emphasized. Although this discussion has emphasized the use of continuous nebulization therapy, additional supportive procedures may be needed in the over-all management of abnormal ventilation. Samson and Dugan[34] have presented techniques and the indications for their use in the support of ventilation. When structural deficiencies are severe, mechanical means have been applied[24] to overcome hypermobility of the chest cage.

SUMMARY

1. Abnormal pulmonary ventilation has been demonstrated to be responsible for almost half of the deaths of premature infants during the neonatal period.

2. A high percentage of these deaths is caused by peripheral block of the bronchopulmonary tree.

3. The rationale of the use of continuous nebulization therapy combined with postural drainage is outlined for the management of deficient ventilation.

4. Apparatus and techniques are described whereby an oxygen-rich supersaturated atmosphere may be combined with incubator care.

5. The component parts of aerosol solutions are discussed with suggestions for their use and the response to be gained.

6. The theory for the role of wetting agents in aerosol solutions is outlined in relation to the cause of respiratory tract obstruction.

7. An essentially new method of supporting hydration in the premature infant has resulted from use of supersaturated atmosphere.

8. With proper attention to details of technique as described, the problem of bronchopulmonary obstruction may be approached effectively.

9. The technique of continuous nebulization described appears to be a valuable adjunct to the total control of this problem.

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NEWER CONCEPTS OF PREMATURE CARE

W. L. CRAWFORD, M.D.

Today's treatment of the premature infant is the best the world has ever known. It is constantly improving, but it is not good enough. Any baby born weighing under 1000 gm. with a survival rate of about 5 per cent, or weighing 1000 to 1500 gm. with a survival rate of 35 per cent, would agree to that statement. An infant weighing 2000 to 2500 gm. has a survival rate of 94 per cent.

How good is today's treatment, as compared to yesterday's? Arey and Dent[1] say that the mortality rate in the first year dropped 67 per cent during the period from 1915 to 1948. The drop in the neonatal period is only 50 per cent, and Bundeson[2] states that 69.8 per cent of neonatal deaths in 1951 were in premature infants.

Great credit is due to the general practitioners, obstetricians, pediatricians, pathologists and others for this remarkable drop. Yet the 1946 report of 74,849 stillbirths and 79,079 neonatal deaths gives doctors and mothers a challenge that cannot be ignored. And it is not being ignored. By more careful, earlier and more regular prenatal care, many who would have been stillborn are born alive, and many prematures are carried further along in pregnancy, making them "less premature" as Parmalee[10] aptly phrases it. This dramatically increases survival rate.

RATIONALE OF PRENATAL CARE

What is done by prenatal care to help the infant? Medical care of cardiac disease, hypertension, diabetes, syphilis and other infections, erythroblastosis and other forms of anemia, the use of hormonal and vitamin therapy, nutritional and bed rest therapy are a partial list of the things to be done to decrease the number of stillbirths and early prematures.

Chemical analyses of the blood often indicate therapy of hypoproteinemia, hyperemesis gravidarum and anemia and, according to Heinemeyer,* will, "if not prevent prematurity, at least bring the patient into the delivery room in better physical condition, and lower the incidence of eclampsia."

The obstetrician of today is alert to avoid intranatal dangers to the premature, such intracranial injuries as hemorrhage, or anoxia whether from placental pathology, cord compression, anesthetic or drug depression.

TREATMENT AT BIRTH

All these things are helpful up to the time of birth. What, then, can be done after birth, when the parasitic existence of the infant is ended and he depends on his own vitality plus the help of nurses and doctors?

First the obstetrician, noting the size and condition of the infant, cuts the cord early or late, depending on his estimate of the value to the infant of extra blood from the cord and placenta. At the precise moment of cutting the cord, placental exchange of gases abruptly stops forever, and the lungs must function or death ensues.

To help breathing, amniotic fluid is drained from the respiratory tract by the head-down position. A tracheal catheter, laryngoscope or bronchoscope is used or not, according to local custom and the presence or absence of trained personnel; so-called mucus plugs are seldom, if ever, removed by them. Drugs are of little value. Mechanical devices have enthusiasts, but the general attitude towards their use is one of caution.

The premature is promptly put in a warm incubator, in the prone position, head down, on an inclined plane of at least 15 degrees to promote postural drainage.

OXYGEN

The constant, even flow of oxygen should be maintained, properly humidified. It should not be a hit or miss affair, and its withdrawal should be gradual. Certain recent work indicates that fetal hemoglobin can handle oxygen with about the same efficiency as adult hemoglobin. This is contrary to usual beliefs and some teaching.

Edith Potter's work describing the gradual transition of capillary loops from interstitial locale to alveolar air sacs, and the synchronous disappearance of cuboidal epithelium (through which gas exchange is more difficult) at five, six or seven months, makes clear why certain small prematures need oxygen more than others, and why varying amounts of scattered atelectasis are the rule.

* Personal communication.

We have been going through a phase of lavish use of oxygen, and the pendulum is now swinging towards a smaller, steady amount consistent with the infant's well-being.

TEMPERATURE

The incubator temperature should be regulated to keep the infant's temperature between 95° and 98° or 99° F. The tiny infant with large surface area and low metabolism gets along well with mildly subnormal temperatures.

HUMIDIFICATION—MIST

Humidification of the incubator is accomplished by a mist-spray of water alone or by combinations of water with wetting agents and emulsifiers to which aerosol antibiotics and/or vasoconstrictors may be added

Effects of Mist Therapy. Mist therapy prevents dehydration, thins secretions, lowers surface tension, permitting expansion of collapsed air sacs, carries antibiotics, combating and preventing infection, and reduces edema of the mucous membrane. Denton and Ross[4] are enthusiastic about the use of such supersaturation in the therapy of respiratory problems of the premature, such as anoxia, atelectasis and hyaline membrane. Ravenel[11] also favors nebulization of this type of mist. The basic formula of Denton and Ross is well adapted to the premature infant. Alevaire is a well known combination used by many; whenever we use it, we dilute it considerably because of the large amount of sodium bicarbonate it contains. We also use the Mist-O_2-Gen spray described by Denton and Ross.

Vitamin K is given to the mother during labor, or the infant at birth, or both, to prevent hypoprothrombinemia and resultant bleeding.

NURSERY TECHNIQUE

Then the baby is left alone, and one of the advantages of an incubator is that it protects the infant from too much handling.

Nursery techniques should be standardized. "Standards and Recommendations for Hospital Care of Newborn Infants—Full-term and Premature," published by The American Academy of Pediatrics, has just been revised and should be followed.

The length of time the infant is left alone depends upon its size and general condition, the condition of the mother causing premature delivery, and the practice in that particular hospital.

ROUTINE LABORATORY TESTS

Laboratory tests will be done at once if erythroblastosis or hemolytic anemia is suspected—not only Rh tests, but also a Coombs test, blood type and indirect bilirubin tests. The benefit of one or more exchange transfusions in erythroblastosis is lifesaving. Diamond* has recently almost eliminated the dreaded kernicterus by the same procedure in those infants whose indirect bilirubin in the serum is rising above 20 mg. per 100 ml. or more. The peak level in full term infants is at the second day, in prematures at the fourth day, normally.

If a biochemistry laboratory is available, and especially if microchemistry is done, sodium, potassium, chloride, protein, hematocrit, sugar, urea and carbon dioxide and *p*H can readily be done now. Enough cannot be said for the microchemistry laboratory, which enables pediatricians to save many, many prematures that were previously lost. Those in charge of premature nurseries may say, "We have done very well with our premature infants without a microchemistry lab." With this I would heartily agree, but they would do tremendously better *with* a good laboratory of that type. What is also important, they would get a new pleasure and confidence in their work.

FEEDING

What about feeding? And how shall it be done? Weight alone is not an indicator of vitality or maturity; we often see a 3 pound premature who is active, sucks well, and makes you know it will overcome the hazards of early life if given good nursing care and protected from infection. They may be fed by bottle or dropper, and it makes little difference if skillfully done. However, for the premature who is weak, with poor gag reflex and poor sucking, gavage is preferred. It is quicker and less tiring, and larger amounts are given and can be accurately totaled.

The Indwelling Polyethylene Tube

A marked saving of time and greater protection for the infant are afforded by the indwelling polyethylene catheter, if properly used. This recent development has not had as extensive use as it should have, but a fair trial always seems to convince doctors and nurses of its superiority over the older method of gavage, if it is used rightly. The tubing should be 1 mm. in external diameter. The tip of the inserted end should be gently flamed. This is better than rounding the edges with a nail file. Tubing should be sterile (a 1:1000 Zephiran solution is satisfactory). After rinsing with water, it should be inserted intranasally a distance of

* Personal communication.

the "glabella to xiphoid." We usually leave the other end long enough to reach out of the incubator, where it is taped against the incubator, with the end wrapped in sterile gauze. (Some plug this end with a Q-tip.) The infant can then be fed by gravity, without opening the incubator to disturb the baby. Accurate measure of fluids is possible, and the catheter may stay many days without changing. We often use 2 or 3 drops of Paradrene solution intranasally along the tube (in pediatric wards more often than in the nursery) twice a day if the tube is left in a long time. Mucus accumulations along the tube occasionally require reinsertion after cleansing. Nursing time saved is tremendous. When nursing personnel is short, the anxiety about proper passage and withdrawal of gavage tube is avoided. Also in many hospitals, both large and small, the nursery personnel on the evening and night shifts are not as skilled as those on the morning shift.

We owe a debt to Franc Ingraham and his group, who by early tissue tests proved the relative inertness of polyethylene tubing in the body, and to D. V. Jones and E. Wagner of Cincinnati, who stimulated its use in feeding prematures.

Fluid Feeding

It is the general custom to withhold food and fluids from prematures for periods of time varying from twenty-four to seventy-two hours or longer, and the smaller the baby, often the longer the delay. Statistics show that the greatest death rate is in the first few days; those who survive this period have a fair chance to get along anyway. Our greatest opportunity, then, is to do something for the infant during these first few days if we are really going to reduce mortality. Paradoxical as it may seem, the usual teaching of today by the large majority of leading pediatricians and teachers in our schools is to do exactly nothing during this critical period. This was my custom, too, for over twenty-five years, and I probably would still be doing so if it were not for the help of the microchemistry laboratory, which tells us quickly the exact condition of the premature.

The early embryo is largely water in composition, and the percentage of water slowly decreases as it reaches full term. Hence any premature has more water than a full term, and this has fostered the idea that the premature is overhydrated, when it has exactly the amount of fluid normal for its stage of gestation, provided the mother has not been dehydrated by hyperemesis or the like.

Contrary to general teaching, it is our belief that small infants dry out fast and do it at the expense of intracellular tissue. In Clement Smith's excellent book, *Physiology of the Newborn*, he speaks of infants "losing

20% of body weight in 4 days." We have repeatedly observed such weight losses in small infants in twenty-four hours.

An interesting sidelight on the reluctance of teachers to give adequate fluids early is their quick and almost universal acceptance of humidification or mist, which is simply a different way of preventing dehydration, and avoiding the "drying out period of one to three days" which is so widely advocated. Edith Potter showed the capacity of some lungs to absorb water when she made intratracheal injections in an attempt to produce hyaline membrane disease, and found an astounding amount of water quickly and completely absorbed. O'Brien, Hansen and Smith[9] conclude that supersaturated atmospheres "prevent the hemo concentration normally occurring by 72 hours after birth in other infants without oral intake, but not in mist." Certainly mist will largely prevent water loss by the lungs if it is finely enough nebulized.

The usual routine is sterile water or glucose in water or saline solution followed by a milk formula, varying somewhat in different centers. Small, frequent feedings, gradually increased as the infant tolerates them, is the rule. At first the kind of food does not seem to be as important to the baby as it is to the doctor; more important is the amount. Usually about 2½ ounces per pound per day are recommended at the end of a week or ten days, and 40 to 50 calories per pound. Hughes[6] suggests "100 c.c. per kg. in the first few days, and 150 c.c. per kg. at the end of a week." In many babies it will be necessary to give fluids by clysis or intravenously.

In small prematures we start fluids in four to twelve hours, usually by clysis first, but also by polyethylene gavage in twelve hours or less. Water, saline, glucose, lactate, carbonate, and so on, are used according to needs noted by microchemical tests, especially the hematocrit. We do not ease up on fluids until the hematocrit starts to come down, unless edema appears. We try to give up to 70 to 85 cc. per pound per day as soon as tolerated. We do not recommend this plan for blind usage, but only for those fortunate enough to have adequate laboratory control, which tells the infant's condition at all times.

PREVENTION OF INFECTION

Prematures are prone to infection and should be given antibiotics for a period of time to prevent infection in the neonatal period. Stewart Clifford recommends the use of penicillin, intramuscularly, 50,000 units every six hours, and sodium sulfadiazine, 30 mg. per kilogram, often enough to produce a blood level of 10 or 12 mg. per 100 ml. It should be remembered that antibiotics should be aqueous-soluble and that the bacteria encountered in neonatal infections are often different from those at other ages (notably the colon bacillus).

VITAMIN THERAPY

We give a multivitamin aqueous-soluble product daily, starting at the seventh to the twelfth day. Some withhold vitamins for a few weeks, but we do not.

PULMONARY HYALINE MEMBRANE

This disease occurs only in the early neonatal period, principally in prematures, especially those born by cesarean section. A child cries well, and then has marked dyspnea and cyanosis due to the deposit or exudate of a hyaline film as "a lining in the air-sacs." In an early group of eighty-five cases studied by Edith Potter, fifty-seven died within twenty-four hours. It is hoped that a better understanding of the use of the wetting agents and emulsifiers in supersaturated mists will help to dissolve or penetrate this film and prevent the atelectasis which it causes. It is also the custom to aspirate the stomach contents of those infants born by cesarean section.

RETROLENTAL FIBROPLASIA

This is also a recently described disease, being first recognized by Terry of Boston in 1942. It occurs largely in small prematures, developing in the first few weeks or months of life, and the rate is said to vary from 6 to 23 per cent. It accounts for one quarter to one half of the cases of childhood blindness. Although the giving or withholding of vitamins, iron, glandular products such as sterols, and oxygen has been postulated as a factor in its development, there is actually no agreement as to its cause, or satisfactory treatment. An editorial in the April 4, 1953, British Medical Journal indicts oxygen as a cause, claiming that the disease is seldom, if ever, seen in Britain, because they practically never use oxygen in the treatment of their prematures. On the other hand, Szewczyk in this country claims that he can make the condition better or worse by proper use or abuse of oxygen. The symptoms are entirely objective, and a trained ophthalmologist is needed in following these cases during the early weeks.

After the publication of Hepner and Krause[5] on this disease the use of electrolytes such as sodium and chloride in excess amounts was thought to be a possible cause of this condition. Many started to feed formulas low in sodium and chloride. This is losing its vogue, however. Edmund C. Burke[3] of the Mayo Clinic states, "We have abandoned any further attempts to prevent retrolental fibroplasia by prevention of hyperelectrolytemia in premature infants." We ourselves have given what would seem to many to be enormous amounts of salt, with or without des-

oxycorticosterone (DOCA), but have not seen the development of retrolental fibroplasia in those infants so treated.

BLOOD TRANSFUSIONS

Transfusions of whole blood or component parts of blood are given freely in some places, and other areas pride themselves on getting along without the need of transfusions. I am convinced that babies with anemia, infection or hypoproteinemia will do better with proper use of transfusions. Blood should be given in small amounts, not over 5 to 10 ml. per pound, and should be given slowly. Iron cannot be compared to blood in the treatment of prematures whose hematocrit is falling, say below 32 or 33 per cent. Poor results in the use of blood are almost always due to using too much at one time or giving it too rapidly.

MENTAL DEVELOPMENT

This can be told by following to maturity those who survive. It is fitting that the finest and most complete study of this type was reported two years ago by the pediatrician who has done the most for prematures, both by his own treatment and the kindly, yet persistent, encouragement of others. I refer to Dr. Julius H. Hess, the founder and guiding spirit of the Sarah Morris Hospital Premature Station in Chicago.

It seems unbelievable, but Dr. Hess had mental examinations of 272 of 313 surviving prematures whose birth weight was less than 1260 gm. and who were graduated from the Station in 1922 to 1949—a span of twenty-seven years. These were all examined by physicians, and mental development showed 60 per cent normal or superior, and an additional 25 per cent showed "slight deviation." These covered many cases before the era of antibiotics, vitamin and electrolyte therapy as we know it.

Dr. Hess's feat is impressive in view of Douglas and Mogford's article in the British Medical Journal of April, 1953, in which they state that such surveys rarely trace over 40 to 50 per cent of survivors.

ADRENAL INSUFFICIENCY

Many prematures are easily subject to stress and are unable to hold water, sodium and chloride, but may retain an excess of potassium. Jaudon[7] and others have described this syndrome. Thorne has explained the influence of desoxycorticosterone (DOCA) in this condition. The late developmental changes in the adrenal gland make it fascinating to postulate why this might be.

In 1952 Natelson, Crawford and Munsey[8] published a booklet on the "Correlation of Clinical and Chemical Observations in the Immature

Infant," hoping for a new look at our methods of giving fluids, electrolytes, blood, and the like, to prematures and showing in detail the technique of microchemical studies on the infants.

To discuss the syndrome of Jaudon, we used the term "adrenal immaturity" and stated the following:

> The term "adrenal immaturity" is used here to denote a condition resulting in the inability of the infant to hold water, sodium ion and chloride ion, in the face of the administration of these substances in what would be more than adequate amounts for a normal infant of equal weight. There is no unequivocal histological or pathological evidence to support the thesis that the adrenal is involved.

Many doctors do not recognize this condition, and a number of doctors who participated in a Forum discussion* stated that they had not read the booklet or had not seen the condition. Some who had read the booklet obviously had not read the paragraph just quoted. In fact, the following question was used as the title of the Forum: "Does the Premature Infant need DOCA Support?" A good microchemistry laboratory correlated with clinical observation will point out frequent cases of this condition.

The clinical symptoms of this condition are essentially weight loss on apparently adequate intake, a tendency to cyanosis under stress, even mild; simulated obstruction, suggesting pyloric stenosis, although the vomiting is not projectile; diarrhea occurs in some cases. It is imperative that one have the use of a microchemistry laboratory to properly handle these infants.

SUMMARY

In summary, then, we may conclude that we lose too many premature babies and that our greatest opportunity for improvement is in the first twenty-four, forty-eight or seventy-two hours of life. The time-tested principles of good prenatal care, delivery with as little trauma and anesthesia as possible, the immediate drainage of the respiratory tract and the establishment of an open airway, prevention of undue chilling or undue heating, with a minimum of handling, and the judicious use of oxygen should be strictly followed. The value of supersaturated mists has been definitely established.

In addition, we are making a plea for a greater use of the indwelling polyethylene tube, for the proper use of antibiotics, and for an unbiased attitude towards a microchemical evaluation of the infant's hematocrit, electrolytes, and so on, and a more widespread use of the proper electrolytes, blood and other fluids indicated by the laboratory survey.

The conscientious use of these measures by nurses and doctors will help save many premature babies who might ordinarily be lost; it is a great opportunity for us, and we should embrace it.

* See Quarterly Review of Pediatrics, 8:63, 1953.

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CARE OF THE PREMATURE INFANT

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It is the purpose of this review to describe the program for the care of the premature infant currently being carried out by the Department of Pediatrics of the Yale University School of Medicine. This outline obviously represents only one of many possible approaches to this complex problem. Previous papers in this symposium have discussed specific aspects of premature care, especially controversial ones. This paper presents a practical program which is not remarkable for its uniqueness or originality. Although certain minor modifications* have been made in accordance with findings of recent pediatric research, this plan is basically that initiated by Dr. Grover F. Powers twenty-five years ago.[2,8]

The basic principle which underlies this program may be stated quite simply: it is essentially to support the infant who is poorly equipped to exist in the usual environment until he is adaptive enough to be cared for by his parents. The definition of prematurity used on the University Service of the Grace-New Haven Community Hospital is that recommended by Dunham.[5] Any liveborn infant weighing 2500 gm. (5½ pounds) or less is classified as a premature infant. Length of gestation, maturity level as noted on physical examination, body length, sex and race are regarded as aids in determining prognosis, but are not utilized in the determination of prematurity.

In general, the care of the premature may be divided arbitrarily into three somewhat overlapping periods. First is the *emergency phase*, which lasts from birth until about seven days of age. During this time the main problems of the premature are respiration and maintenance of body temperature.[9] Effort is made to provide an adequate but not excessive supply of oxygen and a carefully controlled environmental temperature. The

* Dr. Henry Silver is largely responsible for these changes.

second period may be called the *alimentary phase* and extends from the third to about the twentieth day of life. During this time feedings are begun and increased until there is a constant weight gain. When the infant no longer has respiratory difficulty and is ingesting adequate quantities of food, he may be considered to be in the *growth phase*. During this period he receives sufficient food for an adequate gain in weight in an environment which is relatively free of infectious agents. At the end of this time the infant is mature enough to adjust to an adequate home situation. Although the care during each of these phases is fairly rigidly planned and executed, minor modifications are made to meet specific situations.

EMERGENCY PHASE

A pediatric intern or resident attends all cesarean sections and those vaginal deliveries in which the infant is expected to be small. Armstrong beds are kept in constant readiness in the delivery suite. Resuscitation is carried out by gentle nasopharyngeal suction using a mucus trap and a soft rubber catheter. Oxygen inhalations are then given through a loose-fitting mask. Although laryngoscopy and positive pressure insufflation are avoided as much as possible, occasionally these procedures are life-saving. The studies of Day and co-workers[4] indicate that pressures as high as 30 mm. of mercury may be tolerated if the time of administration is 150 milliseconds or less. These pressure and time relations cannot be obtained by commercial resuscitators now available. In order to prevent aspiration pneumonitis, gastric lavage is performed on all infants born by cesarean section.

All infants who weigh less than 2500 gm. (5½ pounds) or who are too small to be weighed safely are immediately transferred to the Premature Unit. All infants born by cesarean section on the University Service are also kept in the Premature Unit for at least twenty-four hours. Occasionally a vigorous baby weighing between 2250 and 2500 gm. (5 to 5½ pounds) may be cared for in the rooming-in nurseries if the mother wishes to breast-feed the infant. The floor plan of the Premature Unit, which is geographically isolated from the rest of the newborn nurseries, is given in Figure 19. The nurses' station is situated to provide optimal observation of the smaller infants. Individual rooms are used for large prematures prior to discharge, so that mothers may feed their infants without danger of contaminating the rest of the Premature Unit. A separate room is also available for the isolation of infants. Both the clean and soiled utility rooms are serviced from an outside corridor, thereby minimizing the number of hospital personnel entering the nurseries. Room temperature is maintained summer and winter at 82° F. with a relative humidity of 68 per cent. Each cubicle is supplied with oxygen (maxi-

mum pressure, 55 pounds per square inch), compressed air (maximum pressure, 5 pounds per square inch), suction (maximum negative pressure, 25 mm. of mercury) and circulating outside air (atmospheric pressure) for use with the Isolette.

Strict isolation precautions are maintained throughout the Premature Unit. When attending personnel enter, hands and forearms are washed initially for three minutes before a gown is donned; the hands are washed for one minute between visits to infants, and a clean gown is used. The nursing personnel assigned to the Premature Unit have no contact with other hospital or nursery patients. At least one graduate nurse is always in attendance.

All infants weighing less than 1700 gm. (3¾ pounds) and all other infants with respiratory distress are placed in an Isolette. Environmental temperature is regulated between 82° and 88° F. No other attempt is made to sustain body temperature, and this frequently stabilizes at 93° to 98° F. Axillary temperatures are taken every three hours for the first four days and every four hours thereafter.

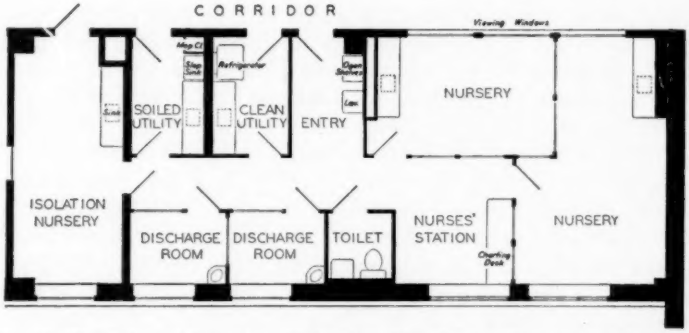

Fig. 19. Floor plan of Premature Unit, Grace-New Haven Community Hospital.

The oxygen concentration has been kept at 40 to 60 per cent (4 liters per minute) and the relative humidity at 65 per cent. At present the optimal oxygen concentration for the small premature infant is not known. Until more experimental and clinical data are obtained, the physician must balance in each case the improvement in respiration, cardiovascular function and cell metabolism which results from oxygen therapy against the possibility that retrolental fibroplasia may be induced in a susceptible infant by a high oxygen tension.

All infants, regardless of weight, who are born by cesarean section or who have respiratory distress are placed in an Isolette equipped with a Vapojette; this apparatus* produces an atmosphere containing distilled

* Air-Shields, Inc.

water particles of small size. This equipment is not completely satisfactory, however, because the particle size of the resultant aerosol is too heterogeneous, and excessive water precipitates on the infant. This supersaturated environment is maintained constantly for the first twelve hours and intermittently thereafter according to the clinical status of the infant. Detergent aerosols are not used, since there is little evidence that atelectasis or hyaline membrane disease in this age group is due to mucus obstruction of secondary bronchi. As with oxygen therapy, the use of high humidity may be a mixed blessing. The evidence is suggestive, but certainly not conclusive, that an environment of high water content may be beneficial to newborns with respiratory distress. However, this same environment unquestionably leads to maceration of the skin and an increased incidence of severe and occasionally fatal skin infections which are frequently due to *Pseudomonas aeruginosa (B. pyocyaneus)*.

Infants who weigh more than 1700 gm. (3¾ pounds) and less than 2250 gm. (5 pounds) and who have no respiratory distress are placed in Armstrong beds. An oxygen concentration of 40 per cent is maintained for at least twenty-four hours and is continued in accordance with the clinical status of the patient. Inhalations of a mixture of 95 per cent oxygen and 5 per cent carbon dioxide are given through a loose-fitting mask in all infants for two minutes every hour for the first twelve hours of life and as needed thereafter. Although the partial pressure of carbon dioxide in arterial blood may be elevated above normal (40 mm. of mercury) in some of these infants, the inhalation of 5 per cent carbon dioxide frequently improves the depth and coordination of breathing and may facilitate the expansion of atelectatic pulmonary areas. Inhalation of this low concentration of carbon dioxide for so short a period cannot lead to narcosis. No effort is made to stimulate the infant physically. Handling, suctioning or examining a feeble infant is minimized, but voluntary movements are unrestrained. Weighing is carried out every forty-eight hours after respiratory distress has disappeared. Chemical stimulants are used only as emergency measures—caffeine and epinephrine in small doses (0.1 to 0.3 cc.) are given intramuscularly or intravenously for respiratory or cardiovascular failure. Although the exact status of hypoprothrombinemia in the etiology of hemorrhagic disease of the newborn is unsettled, vitamin K (5 mg.) is administered intramuscularly to every infant on admission to the premature unit. No oral feedings are given for the first twenty-four to seventy-two hours of life, and then only in the absence of respiratory distress.

Infants weighing less than 1200 gm. (2½ pounds) are usually not fed for forty-eight to seventy-two hours after birth; those weighing more than 1200 gm. are not fed for twenty-four to forty-eight hours. In this way regurgitation and aspiration are avoided. Except in unusual circumstances, parenteral fluids are not administered during this period.

ALIMENTARY PHASE

When the premature infant is no longer in respiratory distress, oral feedings are begun. These initial feedings are designed to meet only a part of the total caloric requirement. Likewise, they supply only a fraction of the water requirement. As a result, body weight falls, and the expanded extracellular volume which is characteristic of prematurity decreases. Severe caloric deficit does not occur, however, since the caloric turnover per kilogram of body weight in the first few days of life is low (40 to 50 calories per kilogram). The water requirement is also relatively low, since it is more closely a function of total metabolism than of body weight or surface area. For these reasons oral administration of small amounts of 5 per cent glucose in water are given initially and then followed later by dilute feeding mixtures. Routine parenteral administration of glucose and electrolyte solutions has been abandoned.

During the first day of oral feedings a total of 50 to 75 cc. of fluid per kilogram of body weight is offered; this supplies 15 to 20 calories per kilogram. On the next day milk mixture is given in an amount which supplies approximately 60 calories per kilogram and 90 cc. per kilogram of water. By the third day of feeding, 110 cc. of milk mixture per kilogram are given; this supplies 75 calories per kilogram. On the fourth day of the feeding routine the premature infant's caloric intake (90 calories per kilogram) is adequate to meet average maintenance requirements. From that time on the intake is increased by small increments every two to three days according to the progress of the infant's feeding behavior. By the twelfth to the sixteenth day of life the infant is usually taking enough calories by mouth to effect a small consistent weight gain (120 to 140 calories per kilogram of body weight per day). Increments in feedings may be suggested by the nursing personnel, but are carried out only by order of the physician.

Bottle feeding is used for most of the premature infants, using a small cross-cut nipple designed by the author and manufactured by the Seamless Rubber Company. This nipple, cap and bottle* are especially suited for terminal sterilization. Dropper feeding is rarely attempted and has been replaced largely by gavage feeding carried out by a graduate nurse. Intermittent gavage with a no. 5 or 10 French soft rubber catheter is occasionally used. More commonly an especially prepared no. 5 French polyethylene catheter† is inserted through the nose and left for no more than four days. Ulceration of the esophagus may result from prolonged use of an indwelling tube, but this is unusual. The time interval between feedings is approximately two hours for infants weighing less than 1200

* Sold under the trade name "Eveready."

† Pharmaseal Laboratories, Glendale, California. Catalogue No. K-32.

gm. (2½ pounds) and three hours for infants between 1200 and 2500 gm. Self-demand feeding has not been attempted here, though presumably successful in some clinics.[6]

The feeding mixture which is used was formulated by Dr. Grover F. Powers twenty-five years ago. It is a cow's milk mixture containing 2 per cent fat to which is added 10 per cent Dextri-maltose by weight. This mixture* at present is diluted with water so that it has a caloric value of 0.68 calorie per cubic centimeter (20 calories per ounce) except for the first several feedings, when the caloric density is 0.34 calorie per cubic centimeter (10 calories per ounce). By the use of this mixture an ade-

TABLE 7. *Composition of Routine Milk Mixtures*

MILK MIXTURE	CALORIES	CARBOHYDRATE GM.	FAT GM.	PROTEIN GM.	ELECTROLYTE mM.	EXCRETABLE SOLUTE mOsm.
			Per 100 cc.			
Half-skimmed*	39	3.6	1.4	2.6	13.4	25.6
Half-skimmed† plus 10% CHO	68	11.0	1.4	2.6	13.4	25.6
			Per 100 Calories			
Half-skimmed	100	9.2	3.6	6.7	34.4	65.7
Half-skimmed† plus 10% CHO	100	16.2	2.1	3.8	19.7	37.7

* 70 gm. of whole milk powder plus 50 gm. of skimmed milk powder plus water.
† 70 gm. of whole milk powder plus 50 gm. of skimmed milk powder plus 100 gm. of Dextri-maltose plus water.

quate intake of water is ensured (145 cc. per 100 calories of food). Approximately 65 per cent of the calories is supplied by carbohydrate, 20 per cent by fat and 15 per cent by protein. Milk mixtures containing less carbohydrate and relatively more protein may be tolerated by most premature infants. There is, however, considerable evidence to support the use of milk mixtures modified by the addition of carbohydrate. The diminished tolerance of premature infants to fat has been adequately demonstrated, as has the optimal level of nitrogen intake. From the standpoint of body physiology, feeding mixtures must be described in terms of content per 100 calories rather than in terms of content per 100 cc. (percentage composition). Thus a milk mixture modified by the addition of carbohydrate has approximately the same nitrogen and electrolyte composition per 100 cc. as the unmodified milk mixture. However, the solute load which must be excreted by the kidneys per calorie ingested is considerably less in the case of the mixture containing added carbohydrate, as demonstrated in Table 7. In view of the limited capacity of the premature kidney to excrete solute without water,[1] it seems ad-

* Dalactum, Mead Johnson Company.

visable to increase the margin of safety by the use of preparations equivalent to the Powers' mixture.

A water-miscible polyvitamin preparation is administered by dropper directly into the mouth after five days of life. This supplement provides 1.5 mg. of thiamine, 0.4 mg. of riboflavin, 7.5 mg. of niacinamide, 0.8 mg. of pyridoxine, 50 mg. of ascorbic acid, 5000 units of vitamin A, 1000 units of vitamin D and 1.5 mg. of tocopherol.

Parenteral fluids are administered only when the oral intake of fluid is less than the minimum maintenance requirement of water or during some disturbance in acid-base balance. Table 8 indicates the minimum and optimum water requirements for prematures at different ages. They are calculated on the basis of changes in caloric expenditure with age. The parenteral fluids which are administered by hypodermoclysis consist

TABLE 8. *Approximate Daily Water Requirement per Kilogram of Body Weight*

AGE DAYS	MINIMUM CC.	OPTIMUM CC.
0– 2	0	0– 40
2– 4	65	80–100
4– 6	75	90–110
6–15	80	120–140
15	80	160–180

of a mixture of equal parts of 5 per cent glucose and Hartmann's isotonic lactate Ringer's solution. Five per cent glucose in water without electrolyte is never administered subcutaneously, since acute reduction in plasma volume always occurs after such a procedure, as Darrow and Yannet demonstrated years ago.[3] Hyaluronidase increases rather than reduces the acuteness of this reduction in plasma volume. Likewise, isotonic electrolyte solution with or without glucose is never used as the sole source of water, since large quantities of water are lost in the urine during the excretion of the excessive load of sodium. Dehydration and hyperosmolarity of body fluids result. Hyaluronidase (50 units per 100 cc.) is used to facilitate absorption of these solutions, which are given in the loose subcutaneous tissues of the back in doses of 20 to 40 cc. per kilogram. Aqueous Zephiran (1:1000) is used to prepare the skin before injection. Careful asepsis must be observed.

GROWTH PHASE

With the feeding of nutriments adequate for growth and weight gain the premature infant is gradually transferred to a less rigidly controlled environment. The concentration of oxygen in the Isolette or Armstrong bed is gradually decreased to 20 per cent when signs and symptoms of respiratory distress such as tachypnea, subcostal retraction, rales or cyano-

sis have completely disappeared and feeding is well established. Usually infants are transferred from the Isolette to the Armstrong bed when body weight reaches 1800 gm. An increase in food intake is ordered with each significant increase in body weight. The caloric intake is thereby maintained at 120 to 140 calories per kilogram a day. Ferrous sulfate is given in a dose of 0.2 gm. a day, beginning at eight to ten weeks of age.

The indications for blood transfusion and chemotherapy are in general the same as for other infants. A complete blood cell count is performed at the end of the first week. The determination of hemoglobin concentration and a white blood cell count are repeated at three week intervals and at the time of discharge. If the hemoglobin concentration falls below 8.5 gm. per 100 ml. and weight gain and feeding are poor, two blood transfusions, each amounting to 10 ml. per kilogram, may be given on successive days.

Chemotherapy is not administered routinely to premature infants. Penicillin and streptomycin have both been administered to all prematures weighing less than 1000 gm., to infants with respiratory distress and to infants born more than forty-eight hours after rupture of the membranes. Procaine penicillin is injected intramuscularly in a daily dose of 150,000 to 300,000 units. Streptomycin is given intramuscularly every twelve hours in doses of 25 mg. per kilogram for not more than seven days. Chloramphenicol or oxytetracycline has been used occasionally intramuscularly as a prophylactic agent in the small prematures. Signs of severe infection due to *Candida albicans* (thrush) or *Pseudomonas aeruginosa (B. pyocyaneus)* must be watched for constantly in infants receiving antibiotics. Blood cultures and cultures of all lesions of the skin or mucous membranes must be obtained promptly in such cases.

When the body weight exceeds 2100 gm. (4½ pounds), the infant is transferred to a bassinet in the graduate section of the Premature Nursery. The time interval between feedings is lengthened to four hours if possible. The mother is urged to come to the nursery and feed the infant with the guidance of a graduate nurse. An appraisal of the home situation of all cases on the University Service is obtained from the Visiting Nurse Association. If the mother is experienced and the home adequate, the baby is discharged from the hospital when body weight exceeds 2250 gm. In the case of a firstborn infant or a questionable home situation, discharge from the hospital is delayed until body weight reaches 2500 gm.

Before discharge a careful ophthalmologic examination is carried out with 1 per cent homatropine hydrobromide—1 drop in each eye—as the mydriatic. Ophthalmologic consultation is obtained in the hospital for all infants whose birth weight is less than 1800 gm. (4 pounds). A follow-up eye examination is scheduled for three weeks after discharge from the hospital.

EDUCATIONAL PROGRAM

Not only the physical development of the premature infant must be considered, but also the emotional responses of his parents. The intern or resident assigned to the Premature Unit visits mothers of prematures frequently during the mother's hospitalization. In this way some parental anxiety may be allayed. After the mother has been discharged from the hospital the father is urged to visit the Premature Unit frequently. At all times the resident staff is available to talk with parents about their infant. In addition, a social worker routinely interviews the family to facilitate social or financial planning. This social worker participates in a weekly conference with all medical and nursing personnel assigned to the Premature Unit. In this conference each infant and family are thoroughly discussed.

A small informal meeting of parents is conducted monthly by one of the pediatric resident staff. The mental and physical development of the premature, his feeding, his future course, and the like, are discussed and positive suggestions for his care are made. In such group meetings, parents frequently pose questions that they would be reluctant to ask the physician if alone.

FOLLOW-UP CARE

The adequate care of the premature, like that of the full term infant, does not cease upon discharge from the hospital. Home visits to service patients are made by the pediatric nursery intern within four or five days after discharge from the hospital. This service provides guidance to the mother in her home and may prevent some serious error in her care of the infant. Its value as a training experience for house staff officers has been discussed by Jackson.[7]

Two to three weeks after discharge all premature babies are seen in an afternoon follow-up clinic by the intern who was responsible for their hospital care. At that time a thorough physical examination is performed and laboratory procedures are carried out as indicated. This clinic visit has not only service value to the patient, but also educational value to the intern.

SUMMARY

The general principles for the care of the premature infant on the University Service of the Grace-New Haven Community Hospital have been given. The physical care of the infant and the educational program for the parents are described. The revised outline for management of the premature is as follows:

REVISED RULES FOR THE CARE OF THE PREMATURE (1954)

1. All newborn babies weighing less than 2500 gm. and all babies born by cesarean section are to be transferred to the Premature Unit.
2. *a.* All newborn babies under 1700 gm. and all cesarean section babies are to be put in an Isolette, with oxygen at 4 liters a minute.
   b. In cases of respiratory distress Vapojette is to be used continuously for the first twelve to twenty-four hours, then six hours on and six hours off, as needed.
3. All newborn babies over 1700 gm. and under 2250 gm. are to be put in an Armstrong bed, with oxygen at 5 liters a minute.
4. All prematures are to be transferred from the Isolette to an Armstrong bed when their weight reaches 1800 gm.
5. All prematures are to be transferred to a bassinet in the graduate section of the Premature Unit when their weight reaches 2100 gm.
6. Routine orders are as follows:
   a. On the Danger List
   b. Suction as needed
   c. Five per cent carbon dioxide and 95 per cent oxygen for two minutes every hour for the first twelve hours
   d. Nothing by mouth for forty-eight to seventy-two hours for babies less than 1200 gm.
   e. Nothing by mouth for twenty-four to forty-eight hours for babies more than 1200 gm.
7. All prematures are to be given parenteral vitamin K (5 mg.) on admission. Fresh blood is to be given at once if there are any manifestations of hemorrhagic disease.
8. Premature infants are not to be stimulated to cry.
9. *a.* Infants weighing less than 1200 gm. are to be fed every two hours.
   b. Infants weighing more than 1200 gm. are to be fed every three hours.
10. The first day of oral feeding (second to fourth day of life) is to be as follows:
   a. Five per cent glucose in water for the first six to eight feedings; total, 30 calories per kilogram.
   b. If tolerated, then: diluted Dalactum (0.34 calorie per cubic centimeter); total, 20 cc. per kilogram.
11. The second day of feeding is as follows: Dalactum (0.68 calorie per cubic centimeter); total, 60 calories per kilogram (90 cc. per kilogram).
12. The third day of feeding should provide 75 calories per kilogram (110 cc. per kilogram).
13. The fourth and fifth days of feeding should provide 90 calories per kilogram (130 cc. per kilogram).

14. The sixth through the ninth days of feeding should provide 100 calories per kilogram.

15. The tenth through the twelfth days of feeding should provide 110 calories per kilogram.

16. The thirteenth through the sixteenth days of feeding should provide 120 calories per kilogram.

17. The seventeenth day of feeding and thereafter should maintain the caloric intake between 120 and 130 calories per kilogram daily.

18. A complete blood cell count is to be done at seven days of age. A hemoglobin and a white blood cell count are to be done every three weeks. A complete blood cell count and urinalysis are to be done at the time of discharge.

19. *a.* A water-miscible multivitamin supplement, 0.6 cc., is to be administered daily after the fifth day.

b. Ferrous sulfate, 0.2 gm. a day, is to be given after the sixtieth day.

20. Penicillin and streptomycin are to be administered if the birth weight is less than 1000 gm. or the membranes have been ruptured more than forty-eight hours.

21. Refer all prematures with a birth weight less than 1800 gm. to the Ophthalmology Clinic three weeks after discharge.

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THE AUTONOMOUS PREMATURE UNIT

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Despite the fact that scientific knowledge concerning the premature has greatly advanced in the last few decades, prematurity still ranks as one of the leading causes of neonatal death.[2,4,5] One of the main reasons for this continued high mortality rate lies in our inability to implement the knowledge that we already possess. The concept of the autonomous premature unit, separate and distinct from either the obstetric nurseries or the pediatric service proper, is at least thirty years old, but has not yet been exploited to its utmost, chiefly because of economic factors.[10] The marked improvement in survival rates which obtains under this type of care and management has been clearly demonstrated by Hess in Chicago and, indeed, wherever these units were established.[3,10,22] It is clearly impossible, however, in the present state of medical economics for voluntary hospitals to construct and maintain premature units without subsidization. Funds must be made available for their operation from either private sources or tax funds, or both. At present tax funds are available for the premature in New York, Illinois, Maryland, Missouri, South Carolina, North Carolina, the Denver area of Colorado and the Territory of Hawaii.

The autonomous premature unit at St. Vincent's Hospital in New York City is one of ten such units servicing the metropolitan area. Prior to the opening of the premature center in May, 1950, our prematures were cared for in the obstetric nurseries, and the advent of the autonomous unit has served to re-emphasize the superiority of this method of care over previous methods of management.

GENERAL CONSIDERATIONS

Economics

The premature unit of St. Vincent's Hospital, with a capacity of thirty, was constructed and equipped at a total cost of 91,532 dollars. One third of this sum was provided for under the terms of the Hill-Burton Act, approximately one third was contributed by private donors, and the remainder of the expense was borne by the hospital. The capital outlay per bassinet was as follows:

Construction	$2593.16
Equipment	461.24

The operating cost of the unit for one year (1951–1952) amounted to $119,819.24, and covered 9364 patient days.[21] We have calculated that the per diem cost is $12.79 when, as occurred in this particular year, 80

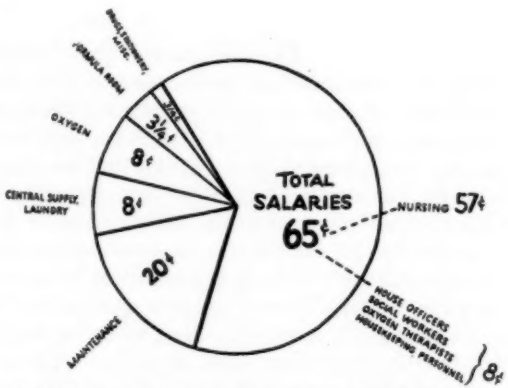

Fig. 20. Allocation of the dollar for care of the premature infant.

per cent of capacity is sustained. This is considerably less than had been estimated when the New York City program for prematures was in the planning stage. At that time (1948) the estimated cost per diem was in the neighborhood of 18 dollars. (We might interject at this point that in this financial discussion we credit salaries, commensurate with their duties and at current wages, to the Sisters, who are unpaid.) State funds, administered by the Department of Health of the City of New York, are used to underwrite the difference between what the family is able to pay and 12 dollars per diem.[21] The unit accepts prematures born in other hospitals and transported to St. Vincent's, and other similar units, by the Premature Transport Service of the City of New York. For reasons which will be discussed in more detail later, these born-out prematures remain in the unit almost twice as long as prematures born in, at a consequently

greater expense. Born-in prematures average 19.8 hospital days at a cost of $254.24. Born-out prematures average 34.5 hospital days at a cost of $341.25.[21] Figure 20 graphically presents the distribution of the premature dollar. The largest item by far is salaries, which represent 65 per cent of the dollar, 57 per cent being allocated to nurses. Attending pediatricians who service the unit receive no remuneration.

PLAN OF UNIT AND EQUIPMENT

The floor plan of the St. Vincent's unit is depicted in Figure 21, and a few of the features require some comment. It is located at a distance

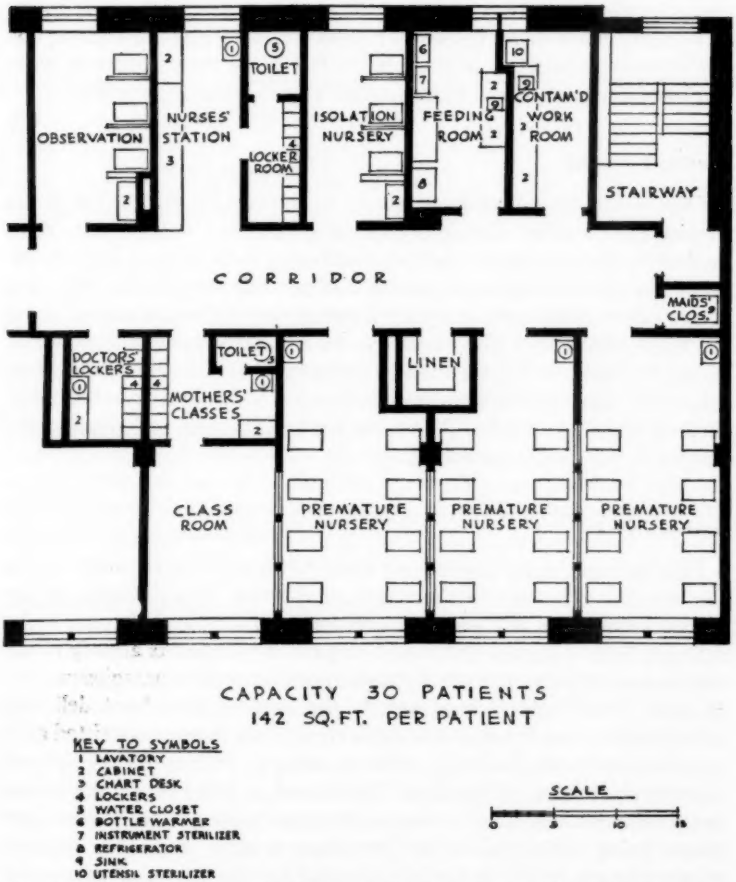

Fig. 21. Plan of premature unit. (Vignec and others: Current Trends in Premature Care. New York State J. Med., Vol. 52.)

from both the obstetric nurseries and the pediatric floors, and was so planned that none but the personnel working with the prematures would enter the area. Colloquially speaking, it is on a "dead end street." The area entitled "Mothers' Classes and Classroom" is now entirely devoted to the instruction of mothers.

Since the unit accepts infants born outside the hospital, an observation nursery was included in our plans. The Feeding Room contains sterile equipment and fresh formulas. Used bottles are returned to the contaminated workroom for preliminary cleansing before being returned to the General Formula Room. Contaminated equipment is sent to Central Supply for sterilization. All infant formulas in the hospital, including those for the premature unit, are prepared in a general formula room.

We have available for the use of prematures one Flagg resuscitator, one Kreiselman resuscitator, nine heated cribs, twenty-two incubators without humidity control and eight incubators with humidity control.

Nursing Personnel

One of the most important factors in the care of prematures is the quality and quantity of nursing care. At present our staff includes eight graduates, nine to twelve students and twelve baby nurses. Two of our graduates have had special training and serve as instructors. We have found baby nurses (with one year of training) quite competent in caring for larger prematures. All nurses are on a five-day week, and graduate nurses and baby nurses are fixed in assignment. It is necessary to obtain nurses who have a keen interest in prematures and who sustain this interest over a period of time. Premature work is exacting and requires the utmost in patience, time and effort.

General Policies

Fifty per cent of the prematures cared for in the unit are born outside the hospital, either in other hospitals or at home. The condition or age of the infant does not preclude acceptance unless he is known to be suffering from a disease that would jeopardize the infants already in the unit: e.g., epidemic diarrhea of the newborn, impetigo contagiosum, and so forth. If prematures born outside the hospital have been delivered within twenty-four hours under sterile conditions, they are admitted after examination to the general premature nurseries. When outside delivery has occurred under contaminated conditions, or if the premature is over twenty-four hours old, he is observed for a minimum of twenty-four hours before being transferred to the premature nursery (Fig. 21). Born-out prematures are mostly in the lower weight groups; as a result our census is composed of approximately twice the expected number of smaller

prematures and slightly more than half the expected number of larger prematures (Table 9).

Whenever possible, the pediatric resident is notified by the obstetric department before a born-in premature is delivered, so that he can be present at the time of delivery and administer to the infant immediately after birth. All infants under 2280 gm. (5 pounds) are brought to the premature unit; larger infants may be cared for in the obstetric nursery if their condition is satisfactory and no special care seems indicated. The latter, however, are listed in the premature statistics.

TABLE 9. *Incidence of Prematurity by Birth Weight Groups*

GRAMS	NEW YORK CITY HOSPITALS (10,244 cases)	ST. VINCENT'S 1950–1952 (675 Cases)*
Under 1000	4.46	8.1
1000–1499	6.83	14.4
1500–1999	17.81	38.0
2000–2499	70.9	43.0

* 332 cases born out.

Pediatric personnel are assigned to the unit on a rotation system and include a qualified attending pediatrician, an assistant resident and an intern. None of these is permitted to serve in contaminated areas during his tour of duty. Pediatricians on the staff of the hospital are permitted to supervise the care of their own cases, and qualified pediatricians not associated with the hospital are generally allowed the courtesy of visiting and consulting. Though the latter are not permitted to order directly, they may do so through the house staff, provided their orders do not conflict unduly with our routine as set forth in the Manual for the Premature Unit. Alterations are made in our routine when they seem indicated by changes in current practices.

SPECIFIC MEASURES

Maintenance of Body Heat

The inability of the premature to adequately regulate his temperature is well known and is attributable to (1) absence of subcutaneous fat, (2) underdeveloped sweat glands, (3) relatively larger surface area in proportion to his weight, and (4) lowered metabolism due to muscular inactivity and inadequate caloric intake.[5] Because of this unstable thermal apparatus, an incubator or heated crib should be available for all prematures—if possible, from the time of birth. An incubator (Armstrong model X4) with a small oxygen tank attached is located in the delivery rooms and the operating rooms. If explosive gases are used in delivery or oper-

ating rooms, the Armstrong model XP, which is explosion-proof, should be used.

The premature is moved from the delivery room to the premature unit, and on arrival is transferred to either a similar incubator, an Armstrong HH model Mark III, or an Isolette.* All prematures under 1800 gm. remain in incubators until they surpass this weight. Very small prematures and those having respiratory difficulties are placed in Isolettes or the Armstrong HH model Mark III, and the larger prematures are cared for in heated cribs, provided they do not seem to need oxygen. Axillary temperatures are taken every three hours while the infants are in incubators, and we consider that temperature control is satisfactory when the range is from 95° to 98° F. (35° to 36.6° C.). Rectal temperatures are taken only when specifically ordered. The incubator temperatures are generally in the neighborhood of 90° F. (32.2° C.), although these must be checked repeatedly, since they are dependent on the frequency with which the incubator is opened.

Prematures born outside the hospital are transferred by the Premature Transport Service of the New York Health Department in portable incubators and are immediately placed in suitable incubators on arrival.[23]

Initiation of Respiration and Oxygen Therapy

Current thought on these two main problems of the premature is in a state of flux. It has been truly said that "we know better what not to do than what to do."[5] Gentleness in handling the respiratory tract of prematures is a prime requisite, and excessive manipulation and instrumentation are to be avoided whenever possible.

The oropharynx is gently cleansed with soft, sterile gauze, and excess mucus is removed by a small catheter with suction bulb and mucus trap (De Lee suction apparatus). Oxygen is made immediately available for infants with respiratory distress and cyanosis. Gentle, manual "artificial respiration" is also used. When severe asphyxia, associated with pallor and flaccidity, is present, the Flagg apparatus is used, and for lesser degrees of asphyxia the Kreiselman machine is the apparatus of choice.[6,11] (It should be noted that all residents in anesthesia, obstetrics and pediatrics are required to attend the lectures on Resuscitation of the Newborn given by the Department of Anesthesiology. These include demonstrations and laryngoscopic examinations on the cadaver. The residents are encouraged to practice repeatedly on cadaver material. Pediatric residents are called for all premature deliveries as soon as possible, for all section cases and for newborns in respiratory distress. The senior residents on the three relevant services are expected to handle all problems of resuscitation

* Air-Shields Co.

except when an attending anesthetist is available.) As soon as the flaccid infant shows any evidence of the return of reflexes or tone, the insufflating tube, which has been inserted by direct visualization, is removed and oxygen is administered by means of the Kreiselman positive pressure mask or by the inhalator mask. Over a two year period mechanical resuscitation was used in thirty-nine instances, an incidence of 5.7 per cent, with a mortality rate of 54 per cent.

In addition to these methods of managing prematures with respiratory difficulties, several other techniques are used. The recent interest in hyaline membrane pneumonia and the mounting evidence of the frequency with which it occurs have stimulated a great deal of investigation in the therapy and possible prophylaxis of this disease.[1] Many observers have noted marked improvement in the condition of prematures and newborns with respiratory distress when placed in an atmosphere of high humidity, up to 90 per cent.[14,22] Consequently, all cases requiring resuscitation, those with respiratory distress, and infants delivered by cesarean section are exposed to this type of environment. High humidities are best obtained in the Isolette or the Armstrong HH model Mark III. More recently we have been interested in the added effect of detergents with high humidity and accordingly have introduced the use of Alevaire.*[18] This is administered in full strength by means of a large reservoir nebulizer (I.E.C. #500 nebulizer [Nebulaire]). An oxygen flow of at least 6 liters a minute is required for the proper functioning of this nebulizer, and excessively high oxygen concentration may be avoided by opening the air vents or by operating the nebulizer with a mixture of oxygen and air. Opening of the air vents does not interfere with the maintenance of a fine mist in the incubator. Our practice is to use Alevaire only on a relatively short-term basis, upwards of seventy-two hours, and then to shift back to high humidity alone. We have experienced no deleterious effects upon the mechanism or finish of our incubators while using Alevaire in this manner, although they have been observed when Alevaire is exhibited over prolonged periods. Proper cleansing of all surfaces is an important factor in maintaining proper functioning of the incubators.

In order to minimize respiratory problems as far as possible, we follow the suggestion of Gellis[7] and practice routine lavage of the stomach contents in cesarean sections. Respiratory stimulants are rarely used with the exception of caffeine sodium benzoate, 2 minims, when severe apnea is present. Delay in offering oral feedings is of great assistance in preventing possible respiratory complications and will be discussed in more detail later.

Oxygen is used freely with cyanotic prematures and those having re-

* An aqueous solution containing 0.125 per cent of oxylated tertiary octophenol formaldehyde polymer with 2 per cent sodium bicarbonate and 5 per cent glycerin.

spiratory difficulty. However, recent work on the effect of high oxygen concentration as one of the etiologic factors in retrolental fibroplasia has made us much more cautious in its routine application.[16] In the absence of respiratory distress, oxygen concentrations *in the incubators* are maintained at a maximum of 45 per cent. In order to do this efficiently, oxygen determinations in the incubators must be made at frequent intervals, since the flow meters are not reliable. At present our oxygen therapist performs these determinations every eight hours by means of Beckman's oxygen analyzer. Oxygen therapy is discontinued as soon as the infant is able to maintain a good color without assistance.

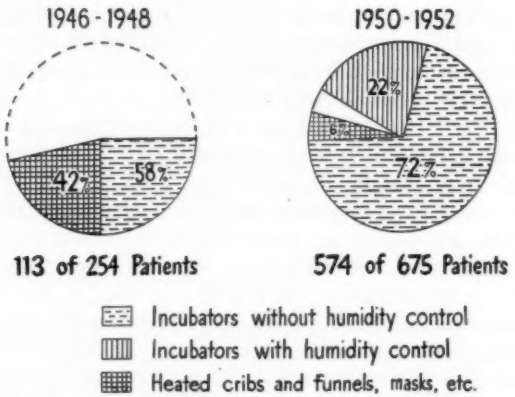

Fig. 22. Methods of (1) maintaining body heat; (2) oxygen therapy; (3) humidity control.

Since the opening of the unit, we have been able to utilize incubators far more frequently than before (Fig. 22). From 1946 to 1948 only 44.4 per cent of 254 patients were given support in the maintenance of body heat and adequate respirations, while in the first two years of the unit's operation, 1950–1952, 84.6 per cent of 675 patients were given respiratory and thermal assistance.[21] The use of funnels and masks has been abandoned, although we still use heated cribs for larger prematures and in the course of weaning the smaller prematures from the respirator. This latter procedure is performed gradually over a period of about four days. The length of time spent in incubators has also been significantly altered. Prior to the establishment of the unit only 8 per cent of incubator babies spent over one week in the incubator, whereas at present 53 per cent are maintained in incubators over one week.[21] The average stay in incubators for born-in prematures is 11.39 days, and for born-out prematures 19.65 days. As we have previously mentioned, this is again a reflection of the fact that born-out prematures are generally in the smaller weight groups.

Nutrition

Second in importance to the problem of respiration is the initiation of feedings and the establishment of an adequate caloric intake. Since fluid requirements are minimal and metabolism is at a low level because of inactivity, there is no pressing need to begin feedings in the first twenty-four to forty-eight hours.[22] The duration of the delay in initiating oral intake is dependent on the weight and vigor of the premature (Table 10).

TABLE 10. *Feeding Techniques Other than by Bottle*

WEIGHT (GM.)	AVERAGE AGE STARTED (HOURS)	METHOD			
		Tube	Gavage	Breck*	Dropper
Under 1000					
1946–1948	13	0	1	1	2
1950–1952	40	4	9	0	3
1000–1499					
1946–1948	14	0	0	1	1
1950–1952	29	23	21	0	2
1500–1999					
1946–1948	13	0	0	5	1
1950–1952	22	20	37	0	4
2000–2499					
1946–1948	14	0	1	0	0
1950–1952	24	1	13	0	0
Total					
1946–1948	14	0	2	7	4
1950–1952	28	48	80	0	9

* Breck discontinued after 1948.

It will be noted that we have gradually increased the waiting period and that the smaller the infant, the longer is the delay.

Our techniques of feeding have also been altered since the opening of the unit. This is in large part due to the qualitative and quantitative improvement in our nursing care. We are much more prone to utilize gavage and tube feeding for small and weak infants than we were in the years before the unit was available (Table 10). Gavage feeding is conducted entirely by trained graduate nurses who use either a no. 8 or 10 French catheter for this purpose. Polyethylene tube feeding, which was introduced in 1950, has proved of inestimable value in feeding small prematures.[20] It reduces some of the risks of gavage feeding and saves considerable amounts of nursing time. The tubing (20 to 22 gauge) is inserted by the resident and allowed to remain in situ for upwards of seven

to ten days. It is customary, however, to change the tubing every three or four days. Before using, it is wise to follow the suggestion of Kunz[12] and treat the gastric end of the tubing with paraffin. Two lateral incisions are made, close to the bottom of the tube, and the tip is then dipped in heated paraffin until it is well covered with a head of paraffin. We have had no complications with paraffin-tipped tubes, but one fatality ascribable to an untreated tube. Bottle feeding is carried out with a "special" premature nipple when the infant is strong enough to take this form of feeding without hazard. The sucking reflex is encouraged in all infants,

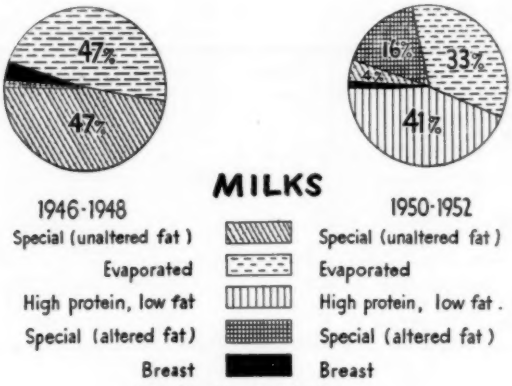

Fig. 23. Types of feeding.

even those in whom an indwelling tube is used, in order to promote the development of a good sucking reflex.

Feeding schedules depend a great deal on the weight and vigor of the premature. Very small prematures are fed by tube and gavage, and the initial oral offering is 2 to 5 cc. of 5 per cent glucose in distilled water with small increases every two hours until the approximate stomach capacity is reached (10 to 30 cc.). Formula is then introduced, and the amount and caloric intake are gradually increased according to tolerance until an optimum of 120 calories per kilogram and a fluid intake of 150 cc. per kilogram per day is obtained. This usually takes about one week. Feedings are offered at two or three hour intervals.

There is a good deal of diversity of opinion as to the type of milk best suited for premature feeding. Good results have been obtained with breast milk and with half skimmed milk-water-carbohydrate mixtures, as well as with other milks.[10,17] Clinical experience and scientific investigations have demonstrated that prematures, particularly the smaller infants, metabolize fat inefficiently.[8,15] It would seem, therefore, that it would be physiologically economic to place small prematures on a high protein-

low fat milk, and accordingly we have, since our unit opened, shifted gradually towards this type of milk (Fig. 23). Breast milk has been all but abandoned, because mothers of prematures are rarely prepared to lactate and it is difficult to obtain, either on a voluntary or commercial basis. Prematures who are gaining slowly are occasionally placed on special milks in which cow's milk fat has been replaced by vegetable fat, identical in iodine number with maternal milk fat. This alteration tends to promote better absorption and utilization.

TABLE 11. *Standard Formulas for Premature Feeding*

	ALACTA (GM.)	BOILED WATER (CC.)	DEXTRI-MALTOSE #2 (GM.)	LACTUM (CC.)	EVAPORATED MILK (CC.)	CAL./CC.
Standard no. 1	8	100				0.35
Standard no. 2	11	100	7			0.75
Standard no. 3A		50		50		0.66
Standard no. 3B		50	4		30	0.65
Conversion no. 1	7	85	5	15		0.68
Conversion no. 2	4	70	3	30		0.69

In order to facilitate the work of the formula room, we use standard formulas whenever possible (Table 11). Our feeding plan, subject to individual variations, is as follows:

1. Standard no. 1 for twenty-four to forty-eight hours, following an initial period of 5 per cent glucose in distilled water for all prematures under 2200 gm.
2. Standard no. 2 until the infant weighs approximately 2200 gm.
3. Conversion no. 1 for twenty-four hours, or longer if necessary
4. Conversion no. 2 for twenty-four hours, or longer if necessary.
5. Standard no. 3A or 3B for (1) after conversion; (2) discharge; and (3) as initial formula for all infants over 2200 gm., following the usual period of glucose water.

Progress through these formulas is gauged by the reaction of the individual infant with emphasis on the stools, weight gain and acceptance. The amount of formula given is dependent on the capacity of the infant and his ability to take feedings, and we tend to increase quantitatively on a demand basis. We have found that not a few infants will take more than the optimum 120 calories per kilogram. The discharge formula (standard no. 3A or 3B) in the majority of cases reaches 3 ounces eight times daily or 3½ ounces seven times.

Vitamins are started on the tenth day, and a water-soluble preparation is used containing in 0.6 cc. (the daily dose) 5000 units of vitamin A, 1000 units of vitamin D, 50 mg. of ascorbic acid, 1 mg. of thiamine, 0.8 mg. of riboflavin and 6 mg. of niacinamide. In using high protein diets, ample amounts of vitamin C should be administered, since Levine[18] has demonstrated that this vitamin plays a role in the metabolism of certain of the aromatic amino acids, phenylalanine and tyrosine. We conse-

quently utilize Dextri-maltose no. 2, which contains 50 mg. of ascorbic acid per 30 gm. The early introduction of vitamins in the diet of prematures is necessary because of incomplete antenatal storage, more rapid rate of growth, small amount of milk taken, defective fat absorption (vitamins A and D), loss of vitamins (especially B and C) in stools because of greater tendency towards loose stools, and a higher susceptibility to infection which increases vitamin requirements.[5] Vitamin K is routinely used in the first three days of life—2.5 mg. intramuscularly as soon after delivery as possible, and 2.5 mg. once daily for two days.

Iron in the form of a solution of ferrous sulfate is begun during the third week of life. The dosage given is between 35 and 75 mg. The utilization of iron at this age is questionable, but it is felt that infants so treated may attain a faster recovery rate of red blood cells and hemoglobin during their first six months of life. It is not effective prophylactically or therapeutically in the anemia of prematurity.[19]

Control and Treatment of Acquired Morbidity

The installation of an autonomous premature unit with improved facilities for isolation of infected cases and the observation of "suspect" cases

TABLE 12. *Incidence of Acquired Morbidity*

	1946–1948	1950–1952	
		BORN IN	BORN OUT
Infections:			
Respiratory	54.2%	17.5%	29.7%
Skin	31.1%	40.3%	35.1%
Other	14.7%	42.7%	35.2%
Total	24%	13.4%	28.3%
Gastroenteritis*	4.7%	10.4%	21.0%

* Includes only cases requiring parenteral support.

provides one of the best methods of controlling acquired morbidity. This is illustrated by the reduction of infections in prematures born in (Table 12). In 1946–1948, when only prematures born in the hospital were cared for, there was an incidence of infection of 24 per cent, and in 1950–1952, born-in prematures had an incidence of 13.4 per cent, despite the fact that the latter were exposed to born-out prematures, 28.3 per cent of whom are infected on arrival or acquire infections after admission. The high incidence of acquired morbidity in prematures born outside the hospital is attributable to (1) greater susceptibility in smaller prematures, (2) more frequent handling, (3) delays in transfer, and (4) deliveries under contaminated conditions. To offset this increased morbidity we are much

more prone to use prophylactic antibiotics in weak infants and those suffering either from respiratory difficulties or other noninfectious conditions which may be complicated by secondary infections. It should also be noted that, in keeping with the higher incidence of acquired morbidity in born-out infants, they receive antibiotics and parenteral support twice as frequently as born-in infants (Table 13). The autonomous unit and the prophylactic use of antibiotics have helped to reduce the incidence

TABLE 13. *Treatment of Acquired Morbidity*

	1946–1948	1950–1952	
		BORN IN	BORN OUT
Antibiotics			
Penicillin:			
Therapy	22	62	121
Prophylaxis	3	52	125
Aureomycin:		11	40
Therapy		11	40
Prophylaxis		3	1
Streptomycin:			
Therapy		34	73
Prophylaxis		8	7
Other:			
Therapy		12	21
Prophylaxis		1	17
Parenteral Fluids			
Clyses	45	45	90
Intravenous Transfusion:	6	14	23
Therapy	12	27	89
Prophylaxis	2	4	7

of respiratory infections, but have not materially affected the incidence of superficial skin infections (Table 12). It is our impression that one of the reasons for this is the more frequent use of incubators and high humidities. Other infections encountered are sepsis, pyelonephritis, osteomyelitis and deep abscesses (noma occurred three times). For a time, gluteal abscesses occurred rather often; because of this, intramuscular injections are given as infrequently as possible and use of the buttocks for this purpose has been discontinued. We confine our intramuscular injections to the lateral aspects of the thighs and the deltoids.

In the treatment of infections of all types, cultures are of the utmost importance. Every effort should be made to isolate the offending organism and to determine its sensitivity to antibiotics. Many of the organ-

isms recovered are resistant to antibiotics to a high degree, and for this reason a variety of antibiotics must be available (Table 14). We have been particularly troubled with resistant staphylococci and *Pseudomonas aeruginosa*. Although determinations in vitro are not always applicable clinically, it is reassuring to use selective antibiotic therapy whenever pos-

TABLE 14. *Antibiotics: Types, Routes and Dosages*

ORAL	
Aureomycin hydrochloride (oral drops)	15–20 mg./kg./day Divided doses every 6 hours
Achromycin (spersoids)	15–20 mg./kg./day Divided doses every 6 hours
Terramycin (oral suspension)	50 mg./kg./day Divided doses every 6 hours
Streptomycin	50 mg./kg./day Divided doses every 6 hours
Chloromycetin palmitate	50 mg./kg./day Divided doses every 6 hours
Erythromycin (pediatric suspension)	35 mg./kg./day Divided doses every 6 hours
Penicillin G (potassium salt)	Prophylactic dose 50,000 units twice daily Therapeutic dose 50,000–100,000 units every 6 hours
INTRAMUSCULAR	
Penicillin G (potassium salt)	50,000–100,000 units every 6 hours
Streptomycin	50 mg./kg./day in 2 divided doses
Polymixin B sulfate	2.5 mg./kg./day Divided doses every 6 hours (Caution: to be used only when indicated by sensitivity tests. Daily urines and predosage and postdosage blood urea nitrogen obtained whenever possible)
INTRAVENOUS	
Terramycin	50 mg./kg./day in divided doses every 12 hours
Achromycin	15–20 mg./kg./day in divided doses every 12 hours

sible. Multisulfanomide preparations are occasionally used (Sulfose, Gantrisin syrup), 130 mg. per kilogram per day in divided doses, every four hours.

The advent of the unit has brought with it an increase in the number of infants who have gastroenteritis severe enough to require parenteral support. This increase is probably due, again, to the larger number of smaller infants. Fortunately we are now in a better position to handle this problem because of an increase in our house staff.

The functional immaturity of renal physiology in the premature and

newborn is well established, so that for clyses we use moderately hypotonic solutions (2.5 per cent glucose in one-half normal saline and one-half distilled water).[9] When there is definite sodium loss, e.g., frequent loose stools, full strength normal saline solution is administered. Excessive intracutaneous tension may cause impairment of circulation and subsequent slough. In order to minimize this possibility, Hyaluronidase (100 viscosity units of 100 cc.) is added to clyses. It is often more convenient to administer intravenous fluids by "cut down" and through a polyethylene tube secured into the veins. The amount of fluid given should be carefully calculated (replacement to equal weight loss in cubic centimeters plus maintenance of 150 cc. per kilogram per day). Because of the relative hypoproteinemia of the premature, calculation alone should not be relied upon, and the hydration should be checked at frequent intervals. The rate of flow should not exceed 15 drops a minute, and it may be necessary to stop the infusion at regular intervals, dividing the total daily intake into portions which can be safely given in six hour periods. Blood chemistry samples are taken whenever possible as a guide to parenteral therapy.

Blood transfusions are used in the treatment of severe gastroenteritis or infections and in more severe anemia (Table 13). In the absence of constitutional symptoms there is no definite level of hemoglobin demanding transfusion. Failure to gain in weight and listlessness with no clinical findings save an unusually low hemoglobin may well respond to a small transfusion. We occasionally give prophylactic transfusions before discharge when the hemoglobin is below 8.5 gm. per 100 ml. (Table 13). The hemoglobin levels attained by these transfusions are rarely sustained for more than two or three weeks; we feel, however, that they assist the infant in overcoming some of the potential hazards of a change of environment and management.

Ophthalmologic examinations are performed on all infants as soon as their prognosis for survival appears good. Eyegrounds are examined weekly as a routine and biweekly if evidences of retrolental fibroplasia are discovered. Every effort is made to warn parents of the possibility of blindness and to keep them informed regarding the status of the eyes. This is done as tactfully as possible and yet remains one of the most frequent causes of misunderstanding and dissatisfaction between parents and physicians associated with the unit. It is extremely difficult for parents to accept blindness. Unfortunately, with the improvement in survival rates of smaller infants, as well as probably other as yet ill defined factors, this problem is increasing in magnitude.

Parent education begins as soon as the mother is well enough to see her baby. After the first week, parents are asked to visit only during regular visiting hours, which are held biweekly. As soon as the infant is large enough (2000 gm. or over) and is gaining well, the parents are in-

vited to visit the nursery and attend classes. In the classroom the mother is allowed to bathe and feed her own baby under the supervision of a nurse. Methods of preparing formulas and other instructions are given. Prematures are discharged when they weigh 2300 to 2500 gm.

Appointments for attendance at the Premature Follow-up Clinic are made on discharge. Mothers who do not plan to utilize the services of private pediatricians are asked to return in two weeks and then at periodic intervals. Those who do have private physicians are asked to return to the Follow-up Clinic at one month, six months, one year, and two years, chiefly for purposes of record.

RESULTS

The autonomous premature unit at St. Vincent's Hospital has markedly reduced our mortality rates for born-in prematures and has greatly

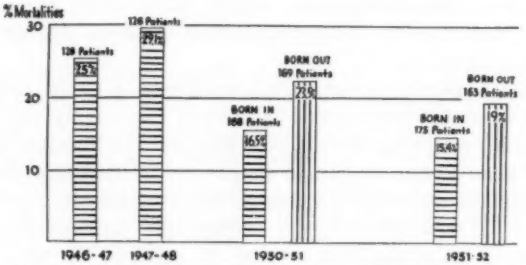

Fig. 24. Mortality rates. Criteria of viability any one of the following: (1) voluntary respiration; (2) heart beat; (3) voluntary muscular skeletal movement.

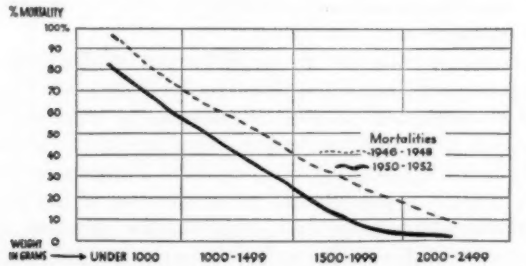

Fig. 25. Mortality rates by weights. Modern methods of care and management of the premature improve the chances of survival 30 to 50 per cent in the 2 upper weight groups and 10 to 15 per cent in the 2 lower weight groups.

improved the chances for survival of born-out prematures (Fig. 24). Born-out prematures, in fact, have a better chance of survival under conditions obtaining in our unit than did prematures born in prior to the opening of the unit in 1950. Our criteria of viability are strictly followed;

consequently we have included in our data prematures who, for all practical purposes, are nonviable—those with only brief respirations, occasional heart sounds, and so on.

The greatest improvement in mortality has occurred in the two upper weight groups (Fig. 25). In the 1500 to 1999 gm. weight group the mortality rate fell from 33 per cent in 1946–1948 to 10.6 per cent in 1950–1952. In the 2000 to 2499 gm. weight group it fell from 7.2 per cent to 2.7 per cent. There has been not nearly as significant a weight drop in the

TABLE 15. *Mortality Rates by Ages*

AGE	1946–1948	1950–1952
Under 24 hours	69.0	54.8
24–48 hours	15.0	19.3
3–7 days	4.1	14.5
Over 7 days	10.8	11.0
Number of deaths	73	126
Patient totals	254	675

lower groups. In prematures under 1000 gm., which include many nonviables, the mortality rate has fallen from 94.9 per cent to 82.5 per cent, and in the 1000 to 1499 gm. group from 57.7 per cent to 43.1 per cent.

Deaths occurring in the first few days of life are still significantly high, particularly in the first twenty-four hours, when over 50 per cent of all deaths occur (Table 15). It may be that improved methods of early management will alter this picture.

CONCLUSIONS

Improvement in the care of the premature is one of the established methods of reducing neonatal mortality rates. The autonomous premature unit accomplishes this objective by providing more adequate space and equipment, superior nursing care and the standardization of techniques and procedures.

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A DEVELOPMENTAL STUDY OF PREMATURELY BORN INFANTS WEIGHING 1250 GRAMS OR LESS AT BIRTH

(*With Special Reference to Those Eighteen Years of Age and Older*)

JULIUS H. HESS, M.D.

Previous reports published in 1949 and 1953 covered small infants with birth weights of 1250 gm. or less who became patients in the Premature Infant Station of Sarah Morris Hospital of Michael Reese Hospital. In the first report we covered all infants admitted between 1922 and December 31, 1949, and in the second report were included all infants received from 1922 through December 31, 1951. In this report we are including all infants received from 1922 through December 31, 1953 (Table 16). For the present report the 1250 gm. weight as the upper limit for the smaller infants was selected arbitrarily. In the 1949 report we included twenty infants with birth weights between 1250 and 1260 gm., but, to simplify a comparison of results obtained in other clinics, in this report we are dividing all our premature infants into weight groups of those weighing 1000 gm. and less and those weighing from 1001 to 1250 gm.

One frequently reads in the public press of the birth of one of these small infants, and occasionally its early progress is reported, but usually its ultimate development is left to the imagination. This, together with the fact that we must all answer the question whether these very small

From the Premature Station at Sarah Morris Hospital.

Credit for the completion of this report should go to the Dr. Louis S. Robins Memorial Foundation.

premature infants are worth saving, encouraged us to believe that a *long-range study of our smallest babies would be of instructive interest.* We are therefore presenting the history of our oldest graduates, all of whom at this time are eighteen years of age or older, with as true an estimation of their physical growth and mental development as possible, as well as the family history of those who are married.

TABLE 16. *Incidence and Fate of Prematurely Born Infants, 1922–1953*

WEIGHT (GM.)	TOTAL	GRADUATED	PER CENT GRADUATED	FATALITY RATE IN STATION			
				Under 24 Hr.	24–48 Hr.	48–72 Hr.	Over 72 hr.
Less than 1000	869	125	14.3	504	90	73	77
1001–1250	948	403	42.5	314	98	68	65
1251–1500	1585	1057	66.6	288	87	88	65
1501–2000	3978	3298	82.9	325	116	180	59
2001–2500	2547	2313	90.8	105	43	77	9
Total	9927	7196	72.5	1536	434	486	275

TABLE 17. *Present Status of 90 Infants Born Prematurely*

LIVING	DECEASED	NOT AVAILABLE	TOTAL
53	19	18	90

	MARRIED	SINGLE
Birth Weight, 1000 Gm. or Less		
Females.....	5	5
Males.....	0	3
Total.....	5	8
Birth Weight, 1001–1250 Gm.		
Females.....	11	14
Males.....	4	11
Total.....	15	25

Of these ninety smallest infants, fifty-three are still living and are known to us; forty-one have been brought to us for personal interview and photographs, and many of them for repeated examinations and study. Twelve located in distant cities were examined by their own pediatricians or family doctors who transmitted to us reports of their mental and physical development. Their ages range from eighteen years to over twenty-nine years (Table 17).

Of the thirty-seven remaining we have positive knowledge of nineteen deaths, but have been unable up to the present time to obtain positive

information concerning the other eighteen, some of whom may have died. The results of this study are presented in Tables 17, 18, 19 and 20.

In this report our greatest contribution lies in the fact that we are presenting a long-range life history of those of our smallest graduates who have passed the adolescent stage and those known to us to have married. Of these, thirty-five are females and eighteen are males. Among them are five sets of living twins and seven surviving twins. Of the five sets of living twins, both infants of two sets weighed under 1250 gm. at birth and are therefore included in this report.

For many years it was our custom to administer blood intramuscularly at least once to all small prematures in an effort to increase their antibody protection and to improve their nutritional status. In recent years, however, it has been suggested that such blood administration could result in changes in the Rh factor of the recipient's blood so that she might be sensitized in her progeny. This has not been verified as far as the married females in our series are concerned. Of eleven of our married females, we have hospital reports on five, all of whom are Rh positive, and none of the eleven have up to this time borne infants who showed evidence of erythroblastosis or other blood dyscrasias.

Over the years there has been definite skepticism in the minds of some as to the ability of these small infants in later years first to become pregnant and second to deliver full term children. Our findings show that of the sixteen female graduates married, eleven have been delivered of twelve living children; in one instance there was a stillbirth reported, and in a second instance a miscarriage at two months, each occurring in the first pregnancy. Each of them later was delivered of one full term normal baby, which represents all subsequent pregnancies to date. Of the four male graduates married, one has sired three children, two each one child, and one sired none.

The histories of the individual married children, sixteen females and four males, are shown in Table 18, page 682.

Individual comments on these married graduates are as follows:

I.V. (case no. 187) has two children, both born at term, four and a half and three years of age respectively.

R.D. (case no. 160) was graduated from the School for the Blind at Jacksonville, Illinois, and was valedictorian of her class. She was married on the day after graduation to a student from the school, but has no children to our knowledge. R.D. became blind from bilateral retrolental fibroplasia.

R.F. (case no. 2) is Rh positive and has been married four years. She has one son thirty months old, whose weight at birth was 6 pounds, 6 ounces, and one daughter, born February 9, 1954, who weighed 6 pounds, 10 ounces at birth.

M.B. (case no. 33) is Rh positive and has epilepsy, but finished grade school. She has one son fourteen months of age whose birth weight was 6 pounds, 6 ounces, and one daughter, born February 26, 1954, who weighed 7 pounds, 8 ounces at birth.

M.C. (case no. 28) is Rh positive. She finished high school and studied beauty culture. She has one daughter two months of age, who was born at term and weighed 6 pounds, 8¼ ounces.

TABLE 18. *Married Graduates*

INITIALS	CASE NO.	SEX	BIRTH WEIGHT (GM.)	PRESENT AGE (YEARS)	NUMBER OF LIVING CHILDREN
I.V.	187	F	935	28	2
R.D.	160	F	935	21	0
R.F.	2	F	995	21	2
M.B.	33	F	1000	18	2
M.C.	28	F	1050	20	1
A.J.	106	F	1060	28	1
B.W.	102	F	1075	29	1
D.P.	36	F	1075	25	1
E.N.	91	F	1090	27	2
D.R.	56	F	1110	25	2
L.P.	213	M	1130	26	3
C.M.	79	F	1150	21	1
W.M.	47	M	1150	28	1
B.M.	72	F	1195	21	0
A.H.	32	F	1230	20	0
L.H.	92	M	1235	22	1
R.G.	148	M	1240	26	0
M.S.	183	F	1245	25	1
M.N.	65	F	1250	25	0
J.G.	39	F	1250	23	1

Twenty patients have twenty living children, and three others are pregnant at this time (May 1, 1954). One first pregnancy resulted in a miscarriage at two months, and there was one stillbirth at eight months; in these two latter cases both mothers later bore a living child.

A.J. (case no. 106) has one daughter three and a half years of age.

B.W. (case no. 102) has a son who was delivered by cesarean section and weighed 6½ pounds at birth.

D.P. (case no. 36) is Rh positive. She finished high school and has been a counsellor at a day camp. She has one son, four and a half months of age, who was born at term.

E.N. (case no. 91) is Rh positive. She did not finish high school. Her first child was stillborn at eight months; a second child, born one month prematurely, weighed 5 pounds, 4¼ ounces at birth and is now four years of age.

D.R. (case no. 56) is a surviving twin. Her first pregnancy ended in a miscarriage at two months. The second pregnancy resulted in a full term boy who weighed 7 pounds, 14 ounces at birth and is now twenty-seven months old. She is again pregnant and expects to be delivered in October, 1954.

L.P. (case no. 213) served in the United States Navy during World War II. He has three daughters, whose ages are four, two and a half years and one year respectively.

C.M. (case no. 79) finished high school and did secretarial work. Her husband was also a premature. She has a daughter, born April 10, 1954, whose weight at birth was 7 pounds, 12 ounces.

W.M. (case no. 47) is a twin whose twin sister is included in this group. He is a fireman in Chicago. He has one daughter, born at term, who is two and a half years of age.

B.M. (case no. 72) is employed and has no children.

A.H. (case no. 32) attended college for one year. She was married in May, 1953, and is now pregnant.

L.H. (case no. 92) finished high school with good grades. He is now with the United States Army in Korea. He has one son, who weighed 8 pounds, 8¾ ounces at term and is now 3 months old.

R.G. (case no. 148) is a twin (his twin brother weighed 1520 gm., which was overweight for this group, is married and expects a child in February). R.G. served in the United States Army and is now employed at a defense plant. His wife has had no pregnancies.

M.S. (case no. 183) has a son three years of age.

M.N. (case no. 65) is a twin (her twin brother weighed 1350 gm. at birth, which is overweight for this group). Married three years, she has no children.

J.G. (case no. 39) is Rh positive. She completed one year of college. She has a son who weighed 7 pounds, 5 ounces at term and is now twenty-nine months of age. She is again pregnant and expects to be delivered in July, 1954.

Of the unmarried graduates eighteen years of age and over there are nineteen females and fourteen males. Among these the following pathologic conditions exist (Table 19):

TABLE 19. *Pathology among 33 Unmarried Graduates*

INITIALS	CASE NO.	SEX	BIRTH WEIGHT (GM.)	PRESENT AGE (YEARS)	PATHOLOGY
M.M.	34	M	1035	19	Moderately severe spastic (not employed)
E.D.	158	M	1250	22	Mildly spastic (employed)
S.N.	78	M	1240	21	Moderately severe spastic (employed; has university scholarship)
A.M.		M	1155	20	Bilateral cataracts (has had operation)
D.R.	64	F	880	19	Very mild spasticity
A.E.	89	F	990	19	Unilateral retrolental fibroplasia (employed)
M.M.	97	F	1220	19	Impaired vision and hearing
S.I.	199	F	745	26	Emotionally unstable

I spoke earlier of the fact that some changes have been made more recently in techniques used in our new station, but I think emphasis should be placed on one practice that has not changed: we are just as firmly of the opinion now as we were in 1922 that breast milk should be an essential part of the early feeding of the small prematurely born infant. The mothers of the babies who are patients in this station are taught to express their milk in the home and send it to the hospital to be used, or, if this is not possible, breast milk is obtained from wet nurses. Approximately 50 per cent of the breast milk used for our smaller infants is obtained from mothers whose infants are in the station or have been graduated from the station. This has been made possible through visitation to the home by the nurse responsible for follow-up care. These visits to the mother who has been delivered at home are made as soon as possible after admission of the infant. The mother is taught manual expression of her breasts. Except when the mother still has ample milk at the time of discharge of the infant, babies are started on a formula during their last days in the station.

I would further emphasize that throughout the history of our station the oxygen concentration in which the babies have been kept has not usually exceeded 45 per cent, except in times of emergency.

In summary I would point out that of the ninety infants weighing 1250 gm. or less at birth and who have been graduated from the premature infant station, all of whom would be eighteen years of age and older, fifty-three are known to us as still living, forty-one are of average or above average physical development, and approximately forty-six are of average or above average mental development.

TABLE 20. *Estimated Developmental Ratings of 53 Cases*

RATING	PHYSICAL DEVELOPMENT	MENTAL DEVELOPMENT
IV	22	34
III	19	12
II	9	6
I	3	1

Three of the young men served with credit in the Armed Forces of our country during World War II, and seven have been or are now in military service. The twenty married graduates have furnished twenty living children. I give you these statistics in support of our original belief that any effort expended in the care of prematurely born infants is of inestimable value. Nature has been kind to many who did not survive the ordeals of their early days, but it is hoped that with further progress in their care there will result, not only continued lowering of early mortality, but also improvement in the physical growth and mental development of those surviving.

It must be evident to all that in order to present such a report as is here given many persons must have been interested in the welfare of these children. Special mention should be made of Evelyn Lundeen, for twenty-nine years Supervising Nurse in Charge of the Premature Station; Roberta Standard, for twenty-two years Nurse in Charge of Field Service and the Outpatient Clinic; Winifred Witz, for fifteen years Head Nurse in Charge of the Premature Station. Many members of the Infants Aid Society have served for long periods in the outpatient clinics and have been of further assistance in the field service. Full credit must also be given to the members of the Sarah Morris Hospital pediatric attending, resident and intern staffs who have served in the Station throughout the years.

The activities of the Station have been made possible through the financial support and endowments provided by the Infants Aid Society of Chicago.

104 South Michigan Avenue
Chicago 3, Ill.

PREMATURE GROWTH RECORD

EVERETT A. NITZKE, M.D.

The daily weights of forty-five healthy premature infants were plotted against a pound-and-ounces scale. By using the resulting curves, an average curve was drawn to correspond to every half pound of birth weight to demonstrate weight gains.

The time interval was extended to ninety days, the approximate period required for 2-pound prematures to reach the discharge weight of 5 pounds.

This premature growth record closely parallels that described by Dancis and his associates.[1]

With continued use in this hospital the graph has become most helpful in evaluating the daily progress of each infant, and it is suggested that it be adopted for each premature nursery.

REFERENCE

1. Dancis, J., O'Connell, J. R., and Holt, L. E., Jr.: A Grid for Recording the Weight of Premature Infants. J. Pediat., 33:571, 1948.

From the Children's Hospital of Michigan, Detroit.

5224 St. Antoine Street
Detroit 2, Michigan

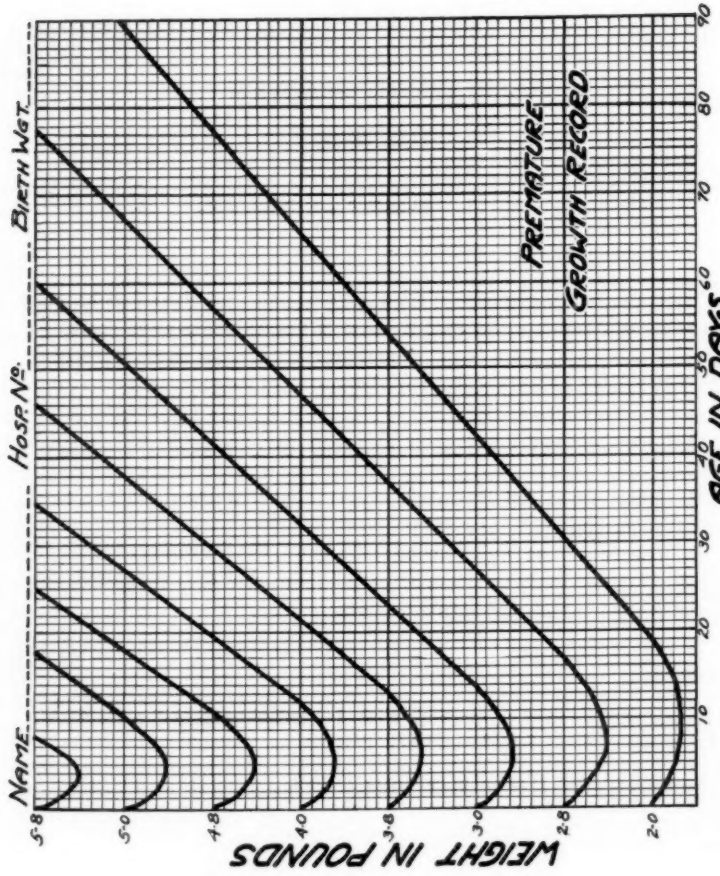

Fig. 26. Premature growth record.

NUTRITION AND NUTRITIONAL DEFICIENCIES AS RELATED TO THE PREMATURE

WINSLOW T. TOMPKINS, M.D.

DOROTHY G. WIEHL, M.A.

The problem of prematurity is generally considered pediatric rather than obstetric; but obviously, without premature labor there would not be a premature baby. Consequently, if a significant reduction in the incidence of premature births, which constitute the greatest hazard to the infant, is to be effected, objective and significant causal evidence relative to this problem is needed.

The concept of the significance of nutrition and nutritional deficiencies in pregnancy recently published[1] pointed out that the various catastrophes of pregnancy are not separate clinical entities which can be expected to respond to some simple specific therapeutic agent. On the contrary, they were shown to be the result of complex, closely interrelated dysfunctions of the individual patient's metabolism and physiology, or, in brief, alterations in nutrition. Therefore, evidence which relates the nutritional status of a patient to the course and outcome of pregnancy, and thus to later catastrophes, is important in that it indicates an approach to these problems which can be preventive, rather than relying upon emergency symptomatic procedures after the catastrophe has occurred.

Data available indicate that the status of the infant at birth is a reflection of the nutritional status of the mother at the beginning of preg-

From the Pennsylvania Hospital (Philadelphia Lying-in Hospital) Nutrition Research Clinic.

The Nutrition Research Clinic is supported by grants-in-aid from the Milbank Memorial Fund, the Williams-Waterman Fund, the National Vitamin Foundation, the Upjohn Company, E. R. Squibb & Sons Company, in part by Mead Johnson & Company, and the Nutrition Foundation.

nancy, as well as during pregnancy; therefore objective evidence by which a patient's status can be evaluated relative to the anticipated stress of pregnancy is important. One of the more significant observations, from a clinical point of view, is the weight of the patient at the time she becomes pregnant. This immediate pregravid weight is an objective observation reflecting the metabolic and physiologic efficiency within the patient. The increased risk of toxemia and other catastrophes to which the obese patient is subject, for example, has received a great deal of attention. From our studies at the Philadelphia Lying-in Hospital, data for markedly underweight patients indicate that they, too, have a greater than average

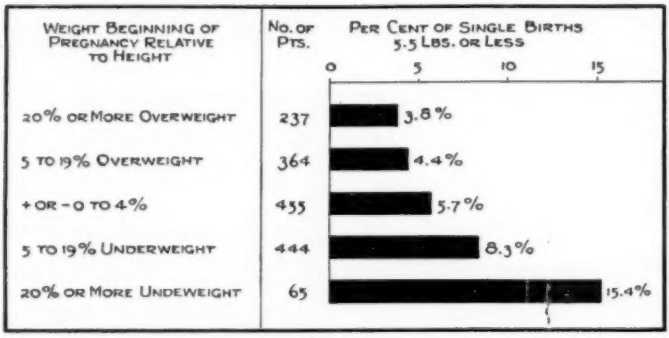

Fig. 27. Premature births relative to immediate pregravid weight.

chance of toxemia and a markedly increased probability of a premature baby.

In Figure 27 immediate pregravid weight status is related to the occurrence of spontaneous premature labor, i.e., to the percentage of single births with a birth weight of 5.5 pounds or less. Here the clinical significance of the initial weight status of a patient in relation to the outcome of pregnancy is clearly indicated. The incidence of prematurity is lower for overweight patients than for those of approximately normal weight, and increases sharply for underweight patients. For all patients 5 per cent or more underweight the rate for prematurity was 9 per cent, compared with 4.8 per cent among patients overweight or approximately of normal weight; the difference between these percentages is highly significant ($P<0.001$).

Only weight at the beginning of pregnancy is considered in Figure 27. For the underweight patients, weight changes during pregnancy and their relation to premature labor are of clinical interest, since it is usually only after pregnancy begins that the physician has an opportunity to influence metabolic and physiologic efficiency as reflected by weight changes.

WEIGHT GAIN IN PREGNANCY

Among the many changes occurring in pregnancy, the result of necessary alterations in metabolism and physiology, one of the most significant is the change in the patient's weight.

An analysis of our data for gain in weight of selected "normal" patients* resulted in a total average cumulative gain in weight during pregnancy of 24 pounds; 21 pounds from thirteen weeks to thirty-nine weeks. The cumulative curve by weeks is shown in Figure 28.

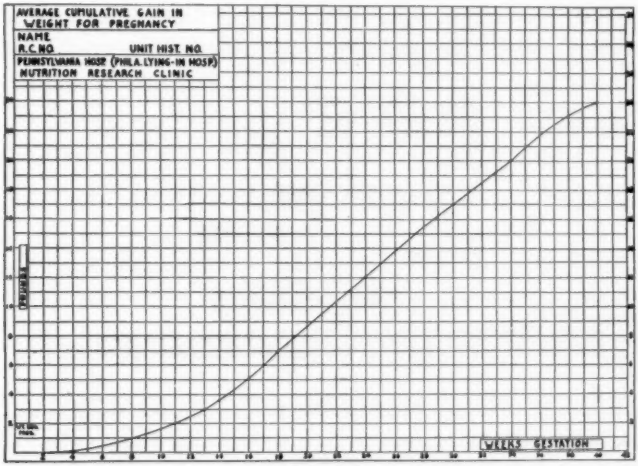

Fig. 28. Average cumulative gain in weight for selected "normal" patients.

The recommended change in weight during pregnancy, as generally stated, varies over such a wide range as to become fantastic. We believe that too much attention has been given to weight as a number, rather than to the objective evidence which a person's weight at any specified time indicates relative to nutritional status. Unfortunately, there has been little factual or objective consideration of the marked and immediate metabolic needs and the resultant physiologic changes which predicate the alterations in weight which should be expected. It is particularly unfortunate that the *first trimester* of pregnancy has been essentially disregarded. It is during this period, the formative period, that the status of the fetus and the placenta is established. Although a normal pattern of gain in weight during the early weeks of pregnancy will not in itself guarantee protection to the patient and her infant, abnormal patterns do

* These patients were free of any major complications of pregnancy or toxic symptoms except for slight edema of the ankles noted once or twice for a few patients. All were within 10 per cent of the standard weight for height.

indicate probable later catastrophe if these early warnings are disregarded.

The significant relationship between the patient's weight status at the beginning of pregnancy and the frequency of premature births is striking; but data on the weight gain during pregnancy of the underweight patients give evidence that this also has an important relation to the occurrence of premature labor.

GAIN IN WEIGHT DURING FIRST AND SECOND TRIMESTERS

The influence on the premature labor rate of different patterns of gain in weight during the first and second trimesters of pregnancy by under-

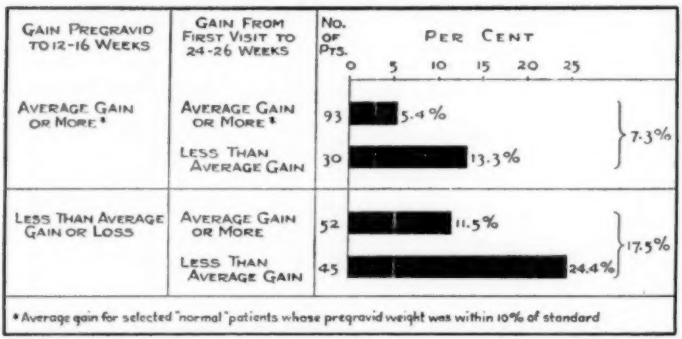

Fig. 29. Premature births according to gain in weight during first and second trimesters.

weight patients and others has been studied for patients who registered with the Nutrition Research Clinic in its first three years, 1947–1949.* In Figure 29 a striking relationship between gain in each of the first two trimesters and the rate of premature labor is shown for patients more than 5 per cent underweight at the beginning of pregnancy. When gain in the first three or four months was less than the average curve of gain, or there was loss in weight, the frequency of premature labor was more than twice the frequency than for the patients with average gain or more. Similar differences in the rates for prematurity are found between groups of patients with less than average gain and average gain or more in the second trimester. Of great importance clinically is the evidence that the underweight patient can be significantly protected if an average gain or greater is established early and maintained to the third trimester.

The significance of the pattern of gain in weight is further demonstrated in Figure 30, which compares underweight patients with those of

* Results of this analysis have been published in detail in Clinical Obstetrics. Philadelphia, J. B. Lippincott Company, 1953, Chap. 9.

normal weight or overweight. For both groups, premature births were nearly three times as frequent among the patients who gained less than average from the first visit to clinic to the end of the second trimester as among the patients who had the average gain or greater. The increased hazard of premature labor for underweight patients is apparent. But for all patients, it is clear that early metabolic and physiologic stabilization of the patient with a steady gain in weight at the average rate could contribute significantly to a reduction in premature labor, which is the highest single cause of infant loss.

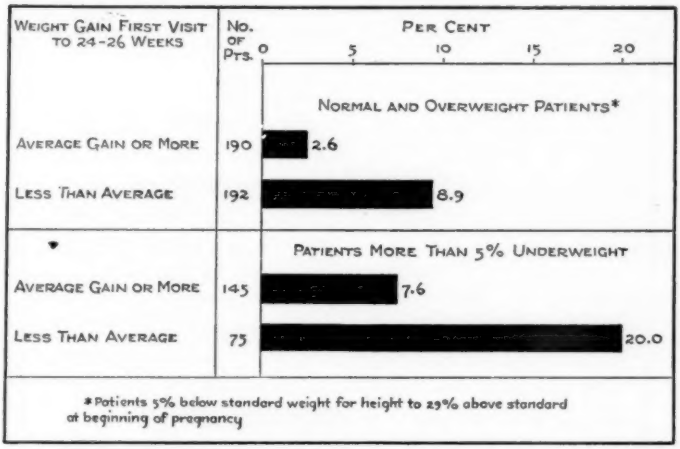

Fig. 30. Premature births and gain in weight in relation to immediate pregravid weight.

The person markedly underweight is obviously not obtaining a sufficient quantity of nutrient intake to maintain standard body weight, and is certainly lacking in the essential nutrients necessary for the support of normal body function. It is good reason to assume that if adequate nutrition is necessary for the maintenance of nonpregnant normal body function, the successful support of pregnancy will require an added intake of essential nutrients. It is equally good reason to assume that this increase in essential nutrient intake cannot begin at a period in pregnancy when a catastrophe is about to occur if adequate protection is to be obtained.

If remedial procedures are to be instituted in an effort to preclude the onset of spontaneous premature labor, every effort must be made as early in pregnancy as possible. The pattern for spontaneous premature labor is established early in pregnancy, particularly for the underweight patient, and by the middle or latter part of the second trimester this pattern cannot be altered. Thus the underweight patient is a hazard not only to herself, but also to her baby.

PREMATURITY BY LENGTH OF GESTATION

The standard for prematurity in the foregoing analysis has been birth weight alone, in accord with accepted practice. Although the length of gestation cannot be estimated accurately, owing to errors in reporting the date of the last menstrual period and variations in time of conception, some indication of the relative maturity of small babies born to underweight patients and to those of normal pregravid weight is of clinical importance with respect to both the patient and the infant. Both birth weight and duration of gestation are considered, therefore, in Figure 31,

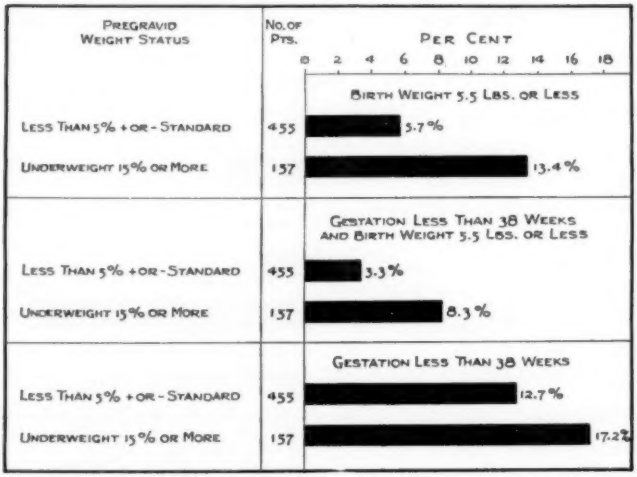

Fig. 31. Premature births for patients of standard weight and underweight relative to birth weight of baby, weeks' gestation, and weight and weeks' gestation.

which gives a comparison of patients of approximately standard weight with patients 15 per cent or more underweight.

The lower section of Figure 31 shows that only a small and not significantly larger percentage of births with an estimated gestation period of less than thirty-eight weeks occurred among the underweight patients. If the percentages on the basis of length of gestation alone are compared with those in the middle section of Figure 31 for gestation and birth weight, it is evident that for both groups the majority of babies with an estimated gestation period of less than thirty-eight weeks weighed more than 5.5 pounds. Some of these probably were immature, but in most instances the gestation period undoubtedly is erroneous.

However, both among underweight patients and among those of standard weight, approximately 60 per cent of the babies weighing 5.5 pounds

or less at birth had an estimated length of gestation less than thirty-eight weeks. Thus, on the basis of both criteria, the underweight patients had a greater risk of premature labor. The rate for premature labor among the patients 15 per cent or more underweight is more than twice the rate* among patients of standard weight whether weight alone is the criterion or weight and gestation.

PRENATAL GAIN IN WEIGHT AND SIZE OF BABY

It has been shown that average or greater gain in weight by underweight patients reduced the percentage of babies weighing 5.5 pounds or

TABLE 21. *Average Birth Weight and Average Crown-Sole Length of Babies and Average Height of Mothers Whose Weight at Beginning of Pregnancy Was within 5 Per Cent of Standard Weight and Those 20 Per Cent or More Underweight*

MEASUREMENT AND PREGRAVID WEIGHT STATUS OF MOTHER	NUMBER	AVERAGE	ST. ERROR OF AVERAGE	SIGNIFICANCE OF DIFFERENCE
Birth weight*				
Mother standard weight	440	7.37	0.046	
Mother underweight 20%+	60	6.69	0.134	$P < 0.001$
Crown-sole length of baby*				
Mother standard weight	379	49.85	0.108	
Mother underweight 20%+	50	48.43	0.271	$P < 0.001$
Height of mother				
Mother standard weight	455	62.0	0.115	
Mother underweight 20%+	65	61.9	0.324	Not significant

* Excludes babies of less than 38 weeks' gestation with birth weight 5.5 pounds or less.

less at birth. It is of interest to examine the effect of weight status of the mother at the beginning of pregnancy and her prenatal gain in weight on the weight and size of all babies.

The average weight of babies born to patients who were 20 per cent or more underweight at the beginning of pregnancy is about 11 ounces less than the average weight of babies of patients of standard weight. As shown in Table 21, the averages were 6.69 pounds and 7.37 pounds.

This difference in weight at birth is due to a statistically significant difference in the length of the babies, and is not the result of greater amounts of soft tissue relative to skeletal size. Most of the babies were measured one to five days after birth, and the average crown-sole lengths

* By weight alone the difference between the percentages of premature babies among underweight and standard weight patients has a statistical probability of less than 1 per cent; by weight and gestation, probability of the difference is 0.01 to 0.05.

are also shown in Table 21. Babies of patients in the underweight group were, on the average, slightly more than 1 cm. shorter.

The patients in each of these weight status groups did *not* differ in height. The average height of those in the standard weight group was 62 inches, and for the patients 20 per cent or more underweight the average was 61.9 inches. Thus, although the length of the baby at birth may be affected to some degree by genetic factors, it appears that the weight status of the mother is a dominant factor affecting fetal growth.

These differences in weight and skeletal length of babies of patients differing widely in immediate pregravid weight status raise the question as to the relation of the prenatal gain in weight to the size of the baby.

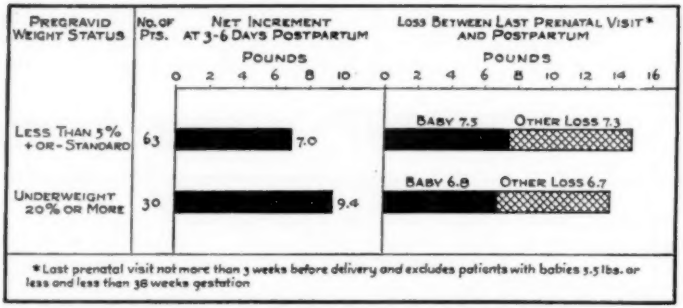
Pregravid Weight Status
No. of Pts.
Net Increment at 3-6 Days Postpartum
Pounds
0 2 4 6 8 10
Loss Between Last Prenatal Visit* and Postpartum
Pounds
0 2 4 6 8 10 12 14 16
Less Than 5% +or- Standard
63
7.0
Baby 7.5
Other Loss 7.3
Underweight 20% or More
30
9.4
Baby 6.8
Other Loss 6.7
*Last prenatal visit not more than 3 weeks before delivery and excludes patients with babies 5.5 lbs. or less and less than 38 weeks gestation

Fig. 32. Birth weight of babies of underweight and standard weight patients relative to net weight increment of mother during pregnancy.

In order to eliminate, as far as possible, the effect of edema on the recorded gain in weight, the comparison of prenatal gain in weight is based on selected "normal"* patients in each group. In addition, only patients are included for whom a postpartum weight three to six days after delivery was available. The postpartum weight makes it possible to separate the total cumulative gain in weight into three categories: the baby's weight, other weight loss at delivery which includes placenta, amniotic fluid and plasma volume change, and also the net increment of tissue mass added to the patient's body weight.

In Figure 32 the average amount of gain in weight identified with each of the three categories is shown for "normal" patients in the underweight group and the standard weight group. These data show a total average gain to the last prenatal visit over the pregravid weight of 22.5 pounds by the underweight patients and 21.8 pounds by the patients of standard weight. Thus the gain was nearly equal. However, the average weight of the babies of these selected patients differed in about the same amount

* Patients selected as "normal" had no prenatal complications, no toxemia, and no edema except slight ankle edema one or two times for a very few patients, and none had premature babies by weight and gestation.

as for the total groups; that is, the babies of underweight patients averaged 0.7 pound less than those of the standard weight patients.

It is notable that the very underweight patients had a greater net body increment in weight after delivery. Under the stimulus of an increased metabolic rate during pregnancy the underweight patient apparently adds to her own active tissue mass at some sacrifice to the fetus. Consequently there is no indication that a relatively high rate of gain by underweight mothers does increase the size of the baby. The increase in her own tissue mass may afford greater protection to meet the stress of pregnancy.

It may be concluded that the strong association between size of baby and pregravid weight status of the mother operates independently of prenatal gain. Failure to gain an average amount, especially in the first two trimesters, increases the likelihood of premature labor, but greater gain has little, if any, effect on the size of the baby.

THE EFFECT OF NUTRIENT SUPPLEMENTS DURING PREGNANCY ON THE INCIDENCE OF PREMATURE BIRTH

Patients registered in the Nutrition Research Clinic were assigned seriatim to one of four study groups by the statistical staff in a manner which would maintain comparability among the four groups for color, age and gravida of patients. The four primary study groups are as follows: (*a*) control group, no supplement; (*b*) vitamin-supplemented group; (*c*) protein-supplemented group; (*d*) vitamin- and protein-supplemented group.*

Patients in all groups received throughout their pregnancies the same prenatal care and management. Diet instructions were compiled by the nutritionist and supported by supervision and direction of the obstetric staff of the Clinic. The diet used in the research study was marginal and designed to produce a base-line against which supplementation could be expected to show a differential, if such a differential existed.

The vitamin supplements used throughout the study were begun at the time of the patient's first visit to the Clinic. It was recommended to all patients assigned to the vitamin-supplemented groups that they take one capsule three times daily.

This arbitrary level of supplementation was established with the intention of amply meeting the increased needs of pregnancy. It was felt, and experience has indicated, that at least three times the daily minimum allowance for nonpregnancy as recommended by the National Research Council would be required to meet the increased needs of pregnancy. Further, by giving three polyvitamin capsules daily it was intended that this dosage would, for the majority of patients, meet the additional physi-

* The nutrient supplements used in this study were polyvitamin concentrates (Upjohn's Zymacaps and E. R. Squibb & Sons' Theragran); protein concentrate (Mead Johnson & Company's Protenum—nonsupplemented).

ologic stress situations resulting from pregnancy, and demonstrate a differential from the marginal dietary intake, if such a differential existed. This amount of polyvitamin dosage was not intended to be therapeutic, but rather, supplemental in character.

The amount of protein supplement recommended (8 ounces by volume) produced 50 gm. of high biologic protein in addition to the protein derived from dietary intake. The protein concentrate, except for approximately 1.5 gm. of calcium, was essentially vitamin- and mineral-free. The discussion of protein supplementation should not imply that such a procedure is desirable in the management of prenatal patients. As stated, the

TABLE 22. *Prematurity and Supplemented Diet (Frequency of Single Premature Labors by Specified Weights According to Patients in Control and Supplement Groups)*

BIRTH WEIGHT	NUMBER IN SPECIFIED STUDY GROUP			PER CENT IN SPECIFIED STUDY GROUP		
	Total	Control	Supplements	Total	Control	Supplements
Total births	839	198	641	100.0	100.0	100.0
Total 5.5 lbs. or less	63	22	41	7.5	11.1	6.4
5.1–5.5 lbs.	36	12	24	4.3	6.1	3.7
4.6–5.0 lbs.	15	6	9	1.8	3.0	1.4
2.25–4.5 lbs.	12	4	8	1.4	2.0	1.2

The control group and each supplemented group are equalized as to the proportions that were white or colored and the number of previous pregnancies. The average percentage of colored patients is 22, and the percentages for the four study groups differed by less than 2 per cent.

recommended diet was marginal in character, and it was desirable to evaluate possible benefits from known amounts of protein intake exclusive of other nutrient factors, so far as this was possible. It is the authors' opinion that adequate protective amounts of protein, sufficient to meet the increased needs of pregnancy, can be obtained from dietary sources alone.

It must be pointed out that the maintenance of patients on a marginal dietary intake, to which known amounts of supplements are added, is specifically for the purpose of evaluating the needs for the specific nutrients added. It is not intended to imply that this procedure represents a desirable method of obtaining an optimum nutritional status. The criteria of benefits to patients taking nutritional supplements include improvement in the course of pregnancy, labor, and the status of the baby after delivery.

Among the many criteria of benefits to patients taking nutritional supplements is the premature labor rate. In Table 22 the percentages of single births resulting from premature labor are shown for the control group who did not receive supplements and for those who had either

vitamins or protein, or both, as a supplementation.* The premature labor rate has been 7.5 per cent for all patients; but among those in the control group the incidence is 11.1 per cent compared with 6.4 per cent for those who received supplementation, thus giving the control patients a premature labor rate 75 per cent higher than in the supplemented groups. The difference between the control group and supplemented groups is statistically significant; the probability of a difference as great or greater arising from chance alone is about 3 in 100.

Figure 33 considers the frequency of premature labor in relation to immediate pregravid weight among patients in the control and supplemented groups. Striking differences are apparent, and here again a marked

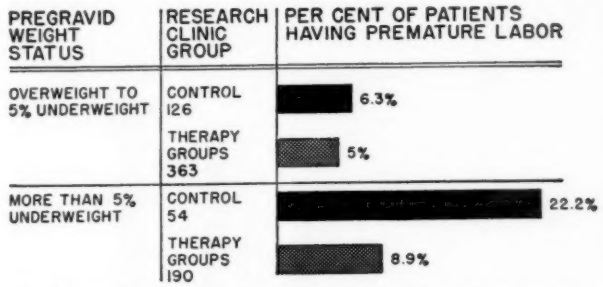

Fig. 33. Premature labor according to pregravid weight and supplementation.

difference occurs between the underweight and overweight patients. In addition, one striking feature should be noted—that an essential difference does not occur in the rates among the control or therapy groups in patients who were standard weight or above. However, among the patients who were more than 5 per cent below standard weight at the beginning of pregnancy, the control group had a rate of premature labor of 22.2 per cent as against 8.9 per cent for comparable patients receiving supplementation; this or a greater difference would be expected from chance alone only once in 100 times. This again indicates the importance of the nutrient reserve factor among these patients, and suggests that supplemental therapy has been effective only among patients underweight.

It is well known that the woman definitely overweight at the beginning of pregnancy has an increased probability of catastrophe. Like the underweight patient, the obese patient is an increased obstetric hazard. This increased hazard is reflected in many ways; consequently the obese patient has been studied separately. Based on the criterion of 5.5 pounds or less indicating a premature birth, obese patients have a strikingly low inci-

* Patients receiving supplements varied widely as to the amounts actually taken, especially with respect to protein. Many patients included in the supplemented groups are known to have taken minimal amounts of protein, and in later analyses of results different levels of supplemental therapy will be considered.

dence of prematures. It is important, therefore, to describe certain differences between obese patients and standard weight patients with respect to length of gestation and weight and size of babies before a discussion of the effects of supplements on the outcome of pregnancy is considered among obese patients.

Length of Gestation

There is a marked tendency for more of the obese patients than of normal weight patients to be delivered later than the estimated time. In Figure 34 the time of delivery relative to the date due for 235 patients

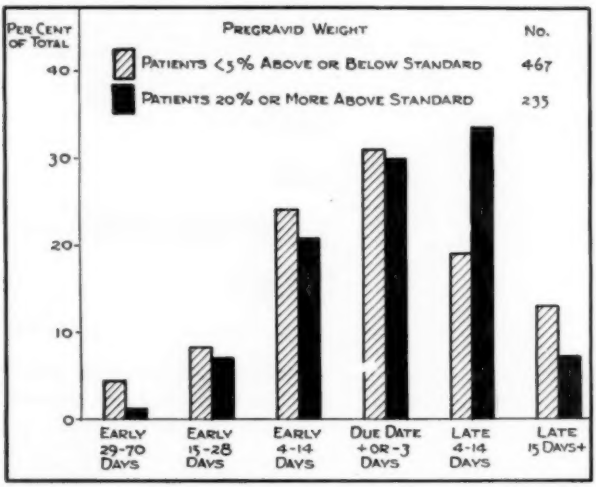

Fig. 34. Time of delivery relative to due date for obese and normal weight patients.

20 per cent or more overweight is compared with that for 467 patients whose weight at the beginning of pregnancy differed from the standard weight by less than 5 per cent.* Although the percentage for delivery within three days of the date due is nearly the same for the two groups, a much larger percentage of obese patients were delivered late and a smaller percentage delivered early than for patients of standard weight.

* Patients were carefully questioned in the clinic as to their immediate pregravid weight and were measured for height without shoes. The standard weight for a specific height and age used is from the Report of the Medico-Actuarial Investigation 1912–1914 up to age twenty-five years. The average weight at twenty-five years is extended to older ages, and the value used is the midpoint of the weight range for women of medium frame published by the Metropolitan Life Insurance Company. One inch was subtracted from heights in published tables to adjust for height without shoes. Although reported weights undoubtedly may be in error a few pounds and height alone is not always an adequate criterion for "ideal" weight, comparisons of groups of patients differing in pregravid weight status should give valid results.

The difference in these two distributions of patients by time of delivery is highly significant statistically.* It may be assumed that errors in reporting date of last menstrual period are approximately equal in the two groups. The metabolic and physiologic factors associated with obesity are apparently related to the factors causing a delayed onset of labor.

Birth Weight

The effect of weight status of the patient at the beginning of pregnancy, which is a reflection of her metabolic and physiologic status, on the weight of her baby is shown in Figure 35.

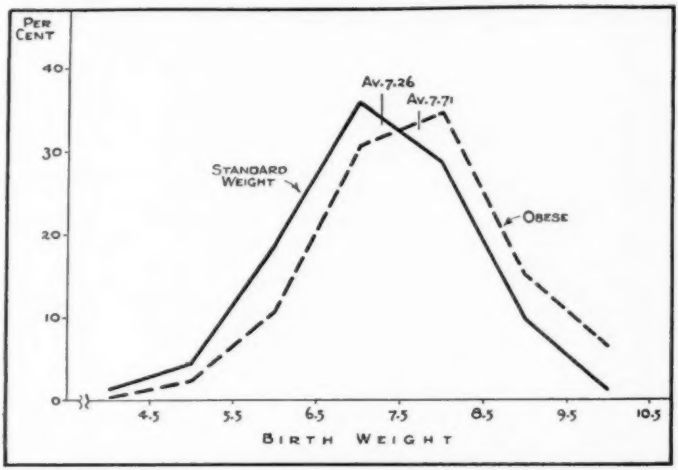

Fig. 35. Distribution of birth weights among standard weight and obese patients.

Patients who were obese had heavier babies than those whose weight differed from the standard weight by less than 5 per cent. On the average, the difference is about 7 ounces (0.45 pound). There is a striking difference in the percentage distributions of birth weights of the babies of obese and standard weight patients, as shown in Figure 35. For the obese patients, 20 per cent of the babies weighed more than 8.5 pounds compared with 11 per cent for the patients of standard weight. Also, only 3 per cent of the infants of obese patients weighed 5.5 pounds or less compared with 5.8 per cent for normal weight patients.

The greater weight at birth of babies of obese patients than of the normal weight patients is not due to the greater proportion of late deliveries among obese patients. If the comparison is restricted to babies de-

* The chi square test of the two distributions gives the following: chi square = 24.176; degree of freedom 5; $P < 0.001$.

livered within seven days of the estimated time for delivery, the average birth weight for 131 babies of obese patients is 7.91 pounds and for 249 babies of normal weight patients is 7.45 pounds, and the difference is the same as for the total groups, i.e., 0.46 pound.

Length of Babies

The greater weight at birth of infants of obese patients is associated with a statistically significant difference in total length between infants of obese patients and those of patients whose weight differed from the standard weight less than 5 per cent.

Most of the babies were measured one to five days after birth, and the average crown-sole lengths are shown in Table 23. Infants of obese patients were nearly 1 cm. longer than those of the patients of a standard weight.

TABLE 23. *Average Crown-Sole Length at 1 to 6 Days after Birth for Babies of Obese and Standard-Weight Patients*

WEIGHT STATUS AT BEGINNING OF PREGNANCY	NUMBER OF BABIES MEASURED	AVERAGE CM.	STANDARD ERROR OF AVERAGE
Above standard weight 20% or more	184	50.65	0.152
Standard weight + or − less than 5%	386	49.72	0.109
Difference		0.93 ± 0.190	$P < 0.001$

Thus the greater weight at birth of the babies of obese patients is due to their greater length and is not the result of a greater mass of soft tissue relative to skeletal size.

SUPPLEMENTS AND DELIVERY TIME OF OBESE PATIENTS

Prolonged labor and inertia is a recognized problem among obese patients. Consequently the tendency for a delayed onset of labor would seem to be another manifestation of the same metabolic and physiologic inefficiency. To test whether this inefficiency is associated with nutritional factors, or with other factors in pregnancy that might be affected by nutrition, the four study groups were compared with respect to time of delivery. This comparison is shown in Figure 36.

The sharp difference in the time of delivery for the patients who received both vitamin and protein supplementation is very evident. Eighty per cent of the patients in this group were delivered within one week of the expected date of delivery compared with 41 to 52 per cent of patients in the other three groups. The experience of the vitamin-protein supple-

mented patients is significantly different from the total obese group (P 0.02 to 0.05), and none of the other three groups differed significantly.

It is important, however, to note that the relatively high percentage of vitamin-protein supplemented patients that were delivered within one week of the expected delivery time is due chiefly to a much smaller percentage of early deliveries among this group. Only 4 per cent of the vitamin-protein supplemented patients were delivered more than one week early compared with 22 to 26 per cent in the other groups. Although

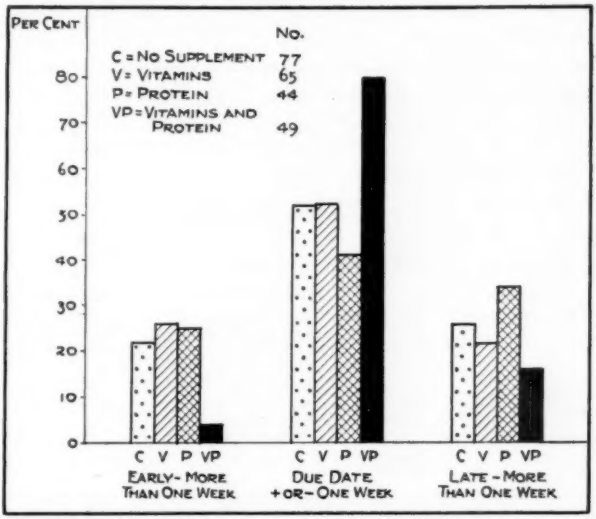

Fig. 36. Delivery time of obese patients in relation to type of supplement.

the percentage of late deliveries was somewhat smaller, 16 per cent among vitamin-protein supplemented patients compared with 22 to 34 per cent for other groups, the difference is not statistically significant.

A complete analysis of the diets of these patients has not been completed; but a preliminary study suggests that there was a tendency for many patients who took the protein supplementation to add this to their regular diet. Therefore, to the extent that the protein supplement provided extra calcium and calories, it should be equally effective for the group taking only protein, as well as for the group taking vitamins and protein. The protein group shows no effect, however, on the date of delivery.

Thus the evidence strongly suggests that when high vitamin therapy was taken and the diet was supplemented with a high biologic protein, there was an improvement in the nutritional status of the obese patient which was reflected in the duration of gestation. Neither protein nor

vitamin supplementation alone had any effect on the duration of gestation.

Prematurity

Since the percentage of patients who were delivered early is smaller for those who received both protein and vitamins, it would be expected that this group would have fewer babies classified as premature on the basis of birth weight of 5.5 pounds or less. There was a total of only seven premature births by the conventional standard of 5.5 pounds or less, and

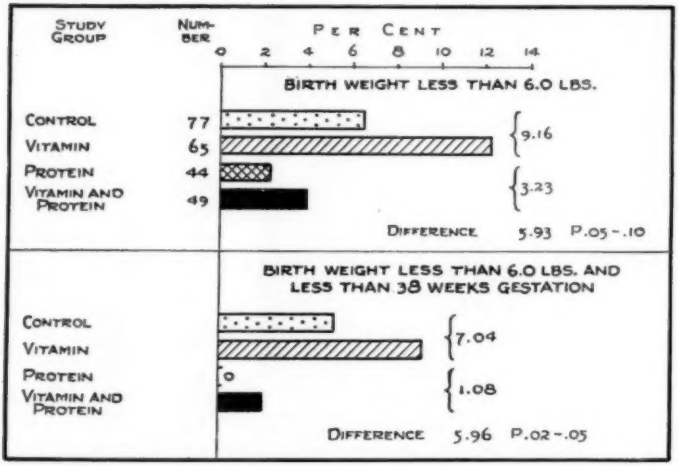

Fig. 37. Frequency of premature birth according to weight standard of 6 pounds and weight and weeks' gestation for control and supplemented patients.

these were distributed among the study groups as follows: three in the control group, two in the vitamin-supplemented group, none in the protein-supplemented group, and two in the vitamin- and protein-supplemented group. All these babies were of less than thirty-eight weeks' gestation except one of the two in the vitamin-protein group, which was born at term to a patient having an extensively calcified placenta. There is no statistical significance to the distribution of these prematures among the four study groups. However, it is suggestive that if the one small term birth is excluded, there were five prematures, 3.5 per cent, among those in the control and vitamin-supplemented groups and only 1, or 1.1 per cent, among those in the two protein-supplemented groups.

Since infants of obese patients are heavier on the average than those of normal weight patients, the probability is high that those weighing slightly more than 5.5 pounds are as premature or immature as lighter

babies born to patients of normal weight. Therefore an arbitrary criterion of less than 6 pounds was taken for prematurity, which increases the usual criterion of 5.5 pounds or less by an amount equal to the difference in the average weights at birth for infants of obese patients and normal weight patients. By the criterion of less than 6 pounds there was a total of sixteen premature babies among the obese patients (6.8 per cent), and eleven (4.7 per cent) were also of less than thirty-eight weeks' gestation. The frequency of premature infants by this weight standard among patients in each of the four study groups is shown in Figure 37.

It is evident in Figure 37 that high vitamin therapy did not prevent babies of less than 6 pounds among obese patients. The rate is higher than for patients who received no supplements, but the difference is not statistically significant. There is a marked decrease, however, in the frequency of such small babies for the patients who took protein or protein and vitamin supplements. As there is no significant difference in the rates for the two groups of patients who received protein supplements, these have been combined and compared with patients in the control group and vitamin therapy group. Although the incidence of babies under 6 pounds is much lower for patients who took protein supplements than for the others, the difference is not statistically significant when weight alone is considered. When both weight and gestation are used, the difference is increased relatively and is moderately significant.

These data support a general conclusion that supplementation of the usual diets of these obese patients with high biological protein resulted in a reduced frequency of very small babies which were probably premature.

SUPPLEMENTS AND SIZE OF BABY

Birth Weight

The average birth weight for all babies in each of the study groups is shown in Table 24. It is clear that a statistically significant difference in the birth weights did not occur. This is important clinically in that it

TABLE 24. *Birth Weight in Relation to Type of Supplement Given to Patients 20 per Cent or More Overweight at Beginning of Pregnancy*

TYPE OF SUPPLEMENT	NUMBER OF BABIES	AVERAGE BIRTH WEIGHT	ST. ERROR OF AVERAGE
Total	234	7.73	0.074
No supplement*	76	7.77	0.139
Vitamins	65	7.57	0.133
Protein	44	7.58	0.139
Vitamins plus protein	49	7.99	0.170

* Excludes one infant weighing 3.2 pounds at birth.

indicates that an improvement in the status of these obese patients through supplementation did not increase the hazard of a heavier baby as compared with the nonsupplemented patients.

Skeletal Size

The average length and chest circumference of babies in each of the study groups is given in Table 25. The differences among the groups are small both for crown-sole length and chest circumference. However, the crown-sole length of babies of the patients who took both vitamins and protein supplements is nearly 1 cm. greater than the average for each of

TABLE 25. *Crown-Sole Length and Chest Circumference of Babies of Obese Patients in Relation to Type of Supplement*

SUPPLEMENT GROUP	NUMBER MEASURED	LENGTH IN CM.		CHEST—CM.	
		Average	St. Error	Average	St. Error
Total*	184	50.65	0.152	32.95	0.127
No supplement	60	50.48	0.246	33.01	0.216
Vitamins	51	50.41	0.315	32.81	0.282
Protein	36	50.58	0.344	32.85	0.266
Vitamins plus protein	37	51.35	0.322	33.16	0.244

* Babies weighing less than 5.5 pounds at birth are not included, since few were measured.

the other three groups. The difference is moderately significant (P 0.01 to 0.05) when the three groups are combined.

This greater length of babies of patients taking vitamin and protein supplements is due chiefly to the small percentage of patients in this group who were delivered more than one week before the estimated time of delivery. The average length of babies delivered not more than one week early or late is 51.31 cm. for the vitamin- and protein-supplemented groups, compared with 50.87 cm. for the other three groups. This difference is not significant.

Birth Weight Relative to Body Build

Further evidence as to the infant status is available when the birth weight of the baby is related to its body build.

The weight of the baby at birth is a function of its skeletal build and amount of soft tissue. It is reasonable to postulate that the nutritional status of the baby may be judged by its weight in relation to body size, just as is done throughout infancy and childhood. By using total length and chest circumference, a predicted weight was calculated for each

baby,* and the difference between this expected weight and the birth weight was determined. A minus difference indicated that the baby was less than the expected weight, and a plus difference indicated greater than the expected weight. These differences are shown in Table 26.

Babies born to patients who received both vitamin and protein supplements were, on the average, about 3 ounces heavier than the predicted weight. The other groups ranged from about one ounce heavier (the control group) to a little less than 2 ounces lighter (the protein only group).

TABLE 26. *Difference of Actual Birth Weight from Expected Weight Estimated from Length and Chest Circumference in Relation to Type of Supplement Given to Patients 20 per Cent or More Overweight at Beginning of Pregnancy*

TYPE OF SUPPLEMENT	NUMBER	AVERAGE DIFFERENCE IN POUNDS	STANDARD ERROR OF AVERAGE
All babies	184	+0.033	0.0386
No supplement	60	+0.075	0.0735
Vitamins	51	−0.025	0.0638
Protein	36	−0.108	0.1782
Vitamins plus protein	37	+0.184	0.0915

Analysis of variance for 4 groups, 3 degrees of freedom: F value is 2.28, and $P < 0.05$.
Analysis of variance of vitamin plus protein group and all others, 1 degree of freedom: F value is 3.89, and P is 0.05.

Individual differences from the expected weight varied over a wide range, from minus 1.4 pounds to plus 1.5 pounds, and are influenced by errors in measurement of chest circumference and length as well as actual differences in amount of soft tissue. This wide variation for individual differences from expected weight applied to all study groups, and an analysis of statistical significance using four groups gives a probability greater than 5 per cent for the observed differences in averages of the groups. However, if the vitamin- and protein-supplemented group is compared with the total experience of the other three groups, statistical significance is borderline at 5 per cent probability.

This finding for the metabolic efficiency of mothers who received both vitamin and protein supplements is consistent with that shown for expected time of delivery relative to date due.

That the babies of patients who received only protein had the poorest

* These calculations were made from multiple regression formulas as follows:

Whites, male and female:
Expected weight = 0.236 cm. length + 0.286 cm. chest circumference — 13.59.
Colored, male and female:
Expected weight = 0.133 cm. length + 0.420 cm. chest circumference — 12.68.

The formulas are based on data for babies born to patients of any pregravid weight status that were rated excellent or good in the first week of life by a pediatrician.

record for weight relative to body size may appear somewhat inconsistent with the previous finding in that only one baby in this group weighed less than 6 pounds. However, examination of the individual records of the patients taking protein supplement only shows that the poor weight status of babies of a few patients, who took less than half of the intended amount of the protein supplement, was responsible for the low average weight for the entire group. Babies of patients who took more than half of the protein supplement had an average deviation from the expected weight of approximately zero (+0.015). Thus, although small immature babies did not occur in this group, the general developmental status was not equal to that of babies whose mothers received both vitamins and protein.

ANEMIA AND PREMATURE LABOR

It is not surprising that anemia, with its attendant anoxia, should have a direct effect on the incidence of premature labor. This represents a

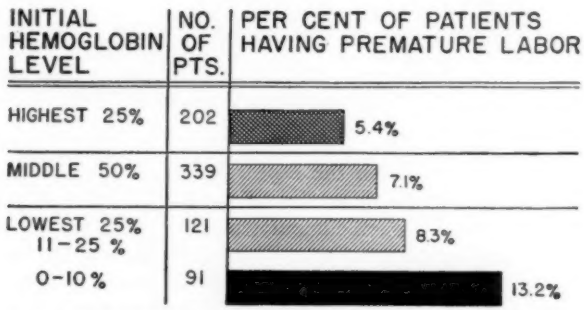

Fig. 38. Premature labor according to initial hemoglobin level.

definite added stress which can affect the organism in many directions. The effect of anoxia on adrenal cortical function may have a direct bearing on the institution of premature labor, and may well represent one of the trigger mechanisms associated with its onset. The interrelation between adrenal cortical function and protein and carbohydrate metabolism, and the necessity for adequate protein levels to maintain normal uterine status have been established. Since anoxia is one of the primary stress factors which can affect adrenal cortical function, it is at least provocative that marked anemia, with the resultant anoxia, should have a direct bearing on the factor or factors incident to the onset of spontaneous premature labor.

In studying the relationship of anemia, or low hemoglobin levels, to premature labor it is necessary to take into account the rapid drop in these levels which occurs during the first half of pregnancy as the result of in-

creased plasma volume. Even the first hemoglobin value is affected, in most cases, unless it is obtained by eight or nine weeks' gestation. Therefore we have classified hemoglobin levels by weeks of gestation, and the distribution of values obtained at any week was subdivided into four groups: the highest 25, the middle 50, and the lowest 25 per cent, which was again subdivided to show the lowest 10 per cent.

Among patients classified according to their earliest hemoglobin value (all were obtained at sixteen weeks or earlier), the premature labor rates among patients with different levels are shown in Figure 38 and Table 27.

TABLE 27. *Prematurity and Hemoglobin Level (Frequency of Premature Labor for White Patients Who Had Different Initial Hemoglobin Values and Received Vitamin and/or Protein Supplements)*

HEMOGLOBIN LEVEL	NUMBER OF PATIENTS	PREMATURE LABOR	
		Number	Per Cent
Total	463	22	4.8
Highest 25%	133	3	2.3
Middle 50%	214	10	4.7
Lowest 25%			
11–25%	68	3	4.4
Low 10%	48	6	12.5

For all patients combined, the premature labor rate rises as the hemoglobin level decreases. This increase in rate, however, is not statistically significant until the lowest 10 per cent level is reached. Among patients in the lowest 10 per cent classification, the premature labor rate increases to 13 per cent, and this rate is statistically significantly higher than for all other hemoglobin levels combined.

SUMMARY

It is clear that adequate nutrition and nutritional deficiencies are critically related to the incidence of premature births. Prematurity is an obstetric problem, not pediatric, which can be significantly altered favorably.

Premature births are inversely associated with the immediate pregravid weight status of the patient, being lowest among overweight patients and increasing sharply for underweight patients.

The hazard of premature labor for underweight patients is much higher if the gain in weight is less than the average gain in the first and second trimesters, and is significantly reduced if an average or greater rate of gain has been established by the middle or latter part of the second trimester.

Babies of underweight mothers are not only significantly lighter, but are shorter than are babies of mothers of approximately standard weight at the beginning of pregnancy.

Underweight patients tend to add more to their own body tissue mass during pregnancy than patients of standard weight, apparently at the sacrifice of the fetus.

Obese patients whose diets were supplemented with polyvitamin concentrate and a protein concentrate showed benefits as compared with obese patients who did not have nutrient supplements or who took only vitamins, or only protein, with respect to several criteria: (1) a significantly larger percentage were delivered within one week of the expected time of delivery; (2) the average crown-sole length of babies was greater as the result of fewer premature deliveries; (3) the birth weight relative to length and chest circumference indicated better development.

Obese patients who received the protein supplements and vitamins, or only protein, had fewer "premature" babies on the basis of birth weight less than 6 pounds and less than thirty-eight weeks' gestation.

A low initial hemoglobin is associated with an increased probability of premature labor; and if patients are both underweight and anemic at the beginning of pregnancy, the probabilities of a premature baby are strikingly high. It is probably not the anemia per se that accounts for the early onset of spontaneous premature labor, but the factor or factors associated with spontaneous premature labor are also related to those resulting in anemia.

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PULMONARY RESECTION IN INFANTS AND CHILDREN

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Pulmonary resection in infants and children is relatively rare. Not many resections are done, even in those institutions actively engaged in pediatric surgery. There are, however, certain diseases of the lungs in which resection is of definite therapeutic value. Improvements in thoracic surgery have made it possible to perform pulmonary resection with safety. There remains the problem of where and when the procedure should be applied.

The occasional pediatric patient with a pulmonary lesion is frequently admitted to hospital with dramatic symptoms of cyanosis and respiratory distress. Correct diagnosis and therapy may be lifesaving. In other instances the clinician may be faced with the dilemma of choosing between conservative and surgical therapy for a pulmonary lesion which is so rare that his clinical experience is limited. We felt that it might be of interest to collect our experience with pulmonary resection in infants and children in order to note the clinical syndromes most frequently encountered and the difficulties involved in their management.

During a twelve year period (1942–1953) forty-seven cases of resectable pulmonary disease were treated. Two cases, previously considered for surgery, responded to conservative management and were not operated upon. Forty-two total or partial lobectomies and two pneumonectomies were performed. Thirteen resections were done as emergency procedures. The rest were done electively. The diseases encountered included bronchiectasis, lobar emphysema, congenital lung cysts, atelectasis and a number of miscellaneous conditions (Table 28).

From the Department of Surgery, Children's Memorial Hospital, Chicago.

TABLE 28. *Summary of Pulmonary Resections Performed in the Children's Memorial Hospital, 1942–1953*

	TOTAL NUMBER	AGES (RANGE)	MEAN AGE	LOBECTOMIES (TOTAL OR PARTIAL)		PNEUMONECTOMIES	EMERGENCY PROCEDURES	ELECTIVE PROCEDURES
				Single	Multiple			
Bronchiectasis	17	2–13 yrs.	9 yrs.	7	9	1	—	17
Lobar emphysema	8	16 days–7 mos.	2–3 mos.	8	—	—	7	1
Congenital lung cyst	10	5 days–13 yrs.	2–3 yrs.	10	—	—	6	4
Atelectasis	5	14 mos.–4 yrs.	2 yrs.	3	2	—	—	5
Arteriovenous fistula (pulmonary)	1	—	7 yrs.	1	—	—	—	1
Bronchial adenoma	1	—	12 yrs.	—	1	—	—	1
Dermoid cyst of bronchus	1	—	9 yrs.	1	—	—	—	1
Fracture of bronchus	1	—	5 yrs.	—	—	1	—	1
Total	44			30	12	2	13	31

BRONCHIECTASIS

It is generally accepted that the presence of isolated bronchiectasis is an indication for excision of the diseased pulmonary segments, whenever possible. Bronchiectasis was found in older children. The youngest patient in this group was two years old; the oldest was thirteen. The average age was nine years. The disease was noted after long episodes of chronic symptoms, including cough, purulent expectoration, repeated upper respiratory infections and pneumonitis. The patients were treated surgically after prolonged conservative management had failed to halt the progress of the disease. The duration of symptoms before operation varied between two and eleven years.

Usually the lower lobes alone were involved. Additional segments of adjacent lobes were excised when necessary. Seven patients required only single lobectomies. Nine had multiple, total or partial lobectomies. Two of these patients with bilateral bronchiectasis had to have operation done in two stages. One patient required total right pneumonectomy. It is interesting to note that, although ten fairly extensive pulmonary resections were performed, none of the bronchiectatic patients was left with serious respiratory impairment.

Conservative management, which has always been the treatment of choice in bronchiectasis, has become infinitely more effective with the advent of antibiotics, and surgery for bronchiectasis has been sharply diminished in our recent experience. Only one patient was operated upon for bronchiectasis in 1953. This patient had symptomatic bronchiectasis localized to the right middle lobe and associated with pancreatic cystic fibrosis. Another patient, referred for excision of the right lower lobe, responded so well to adequate antibiotic therapy that it was possible to forego resection.

CASE I. P.P. was first admitted to hospital on August 8, 1939, at age 6 months, when repair of bilateral cleft palate and lip was begun. She had an uneventful postoperative course and was discharged on September 11, 1939. She was readmitted on October 31, 1939, with a history of cough and fever for 4 days before admission. Pneumonia of the right upper lobe was found and was followed by involvement of the right middle and lower lobes. The patient responded to supportive treatment in the hospital and was discharged on December 5, 1939.

She was followed up in the outpatient clinic and continued to have chronic cough and low grade fever. Atelectasis of the right lower lobe persisted. On March 1, 1940, she was admitted to the hospital, where multiple bronchoscopic aspirations were done and large quantities of thick, green purulent material were removed. The edematous, friable mucosa of the right lower lobe suggested a granuloma occluding the lower portion of the right main stem bronchus. On June 15, 1940, a bronchogram demonstrated bronchiectasis of the right lower lobe. Lobectomy was refused by the patient.

The patient had multiple admissions (1941–1946) for several episodes of pneumonia. Repeated bronchoscopic aspiration yielded copious amounts of purulent material. On December 13, 1946, bronchograms showed marked saccular bronchiectasis of the entire right lung (Fig. 39). No bronchiectasis was demonstrated on the left.

On January 31, 1947, a right pneumonectomy was performed. The chest was closed without drainage. The postoperative course was uneventful, and the patient was discharged on February 21, 1947. Pathologic examination of the right lung revealed extensive saccular bronchiectasis. Since operation the patient has been

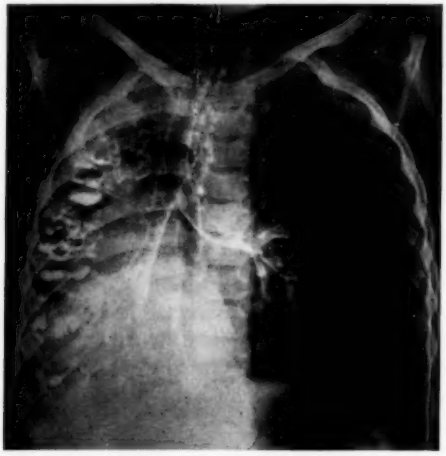

Fig. 39. Bronchogram of a patient, 7 years after the onset of symptoms, showing marked saccular bronchiectasis of the entire right lung. There is no bronchiectasis on the left.

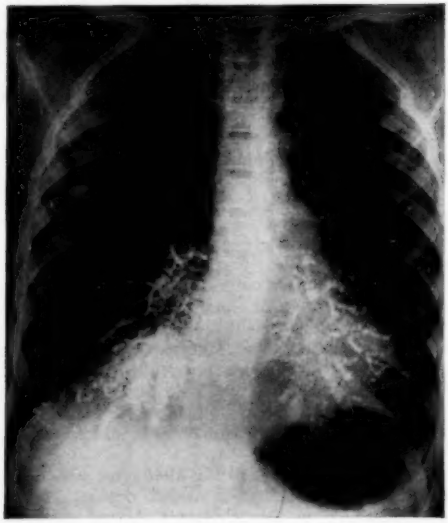

Fig. 40. Bronchogram, after 8 years of repeated pulmonary and upper respiratory infections, demonstrated bilateral basal cylindrical bronchiectasis.

examined at 6 month intervals. She was last seen in June, 1953. Her growth has been normal. Her exercise tolerance permits normal activity.

CASE II. C.B., an 11 year old girl, was admitted to hospital on June 6, 1948, with a history of whooping cough at age 2 years. After the whooping cough she had 2 attacks of "pleurisy" and, at age 4½ years, had severe bronchitis. At age 7 years she had measles followed by pneumonia. She continued to have periodic paroxysms of severe coughing and, for about a year before her last admission, expectorated large amounts of green, purulent material. On physical examination bilateral coarse basal rales and diffuse wheezing were noted. There was a foul odor to her breath. Bronchoscopic examination revealed copious purulent material in both basal lung regions. Bronchograms demonstrated bilateral basal bronchiectasis (Fig. 40). The patient was treated with bronchoscopic aspiration and postural drainage until November 12, 1948, when a right thoracotomy was done. A lower segment of the right lower lobe and the entire right middle lobe were removed. The patient had an uneventful postoperative recovery and was discharged on November 24, 1948. On July 8, 1949, a left thoracotomy was done. The lingula of the left upper lobe and a segment of the left lower lobe were excised. A postoperative bronchogram on October 10, 1949, revealed no residual bronchiectasis.

LOBAR EMPHYSEMA

Emphysema constitutes one of the definite surgical emergencies in infancy.[3,7] The disease occurs within a few days to a few months after birth. The symptoms—dyspnea, cyanosis and cough—may appear suddenly or may develop over a period of several weeks. Roentgenograms of the chest are usually diagnostic. A huge translucent area containing sparse lung trabeculations is noted in the affected lung, and the heart and mediastinum are shifted to the opposite side. Adequate relief calls for immediate exploration. When the chest is opened, the offending lobe is noted to be markedly distended, while the remaining lobes are atelectatic and are pushed into one of the recesses of the pleural space. Removal of the distended lobe permits the remaining lobes to expand as the anesthesiologist applies positive pressure through the endotracheal tube. The displaced mediastinum also promptly moves back to the midline, allowing the contralateral lung to function adequately. The undeveloped ipsilateral lobes can be made to fill about half of the available pleural space at the time of operation. Later they expand to occupy the remaining pleural cavity.

The exact etiology of this condition is not known. Careful gross and microscopic examination of the affected lobe usually fails to reveal any specific "ball valve" mechanism which could be held responsible for trapping inspired air. Chondromalacia of the bronchus has been noted in an occasional case and is considered to be the underlying pathologic lesion in those instances.[3,4]

CASE III. R.G., a 2 weeks old boy, was admitted to hospital on October 13, 1953, with a history of progressively increasing dyspnea and cyanosis for 2 days before admission. Physical examination revealed an alert, fairly vigorous, cyanotic child in acute respiratory distress. Inspiratory retractions of the costal margins and the suprasternal notch were present. The breath sounds were diminshed on the right side

anteriorly and posteriorly. Roentgenograms of the chest showed marked obstructive emphysema of the right upper lobe. There was compression of the right middle and lower lobes and herniation of the upper lobe into the left side. The mediastinal structures were shifted to the left (Fig. 41).

Shortly after admission an emergency thoracotomy was done through the right fourth interspace. An overdistended emphysematous right upper lobe was removed. Immediately after its removal the small atelectatic right middle and lower lobes were expanded under positive intratracheal pressure and the mediastinum shifted back to the midline. The patient's respiration improved. An endothoracic catheter was introduced through the sixth interspace, and the thoracotomy wound was closed. Water-seal drainage was applied to the endothoracic tube for 48 hours. The patient had an uneventful postoperative course and was discharged on October 20, 1953. Postoperative roentgenograms have shown no further abnormalities.

Fig. 41. Preoperative chest roentgenogram showing marked obstructive emphysema of the right upper lobe with herniation of the distended lobe to the left, shift of the mediastinum to the left and compression atelectasis of the right middle and lower lobes. Note the large translucent area with sparse lung trabeculations which occupies most of the right lung field.

CONGENITAL LUNG CYSTS

The management of cysts of the lung in infants and children has been a source of considerable controversy in the literature.[1,6] The differences of opinion have been more apparent than real, however, and have arisen because it is sometimes difficult to determine whether a cyst is congenital or is the sequel of staphylococcal pneumonia. Congenital lung cysts may be asymptomatic until they become infected and exhibit findings that mimic an acute pneumonic process. On the other hand, staphylococcal pneumonias in infants occasionally develop cystic areas during the process of resolution. In both conditions it is advisable to treat the infection with antibiotics, as one would manage any acute lung abscess, permitting the pulmonary inflammatory process to subside. If a diagnosis of postpneumonic cyst can be made by history, multiplicity of cysts or the tendency of the cysts to vary in size from one roentgenographic examination to the other, the treatment of choice is prolonged conservative management, since these cysts ultimately disappear spontaneously. If, however, a soli-

tary cyst persists long after the infection has subsided and shows no tendency to diminish in absolute size, surgical excision should be considered. This is particularly true if pulmonary infection recurs or the cyst enlarges to the point of impairing the patient's respiration.

Ten congenital lung cysts were excised in this series. Generally, they presented three different clinical syndromes: (1) One patient was asymptomatic. The diagnosis was made on a "scout" chest film. (2) Six patients were brought to the hospital with sudden severe dyspnea and cyanosis. They were between five days and five weeks old. Presumably, a ball valve effect had resulted and inspired air was being trapped within the cysts, causing them to expand rapidly and endanger the patient's life. (3) The remaining three patients were older children, six to twelve years of age. They gave histories of repeated episodes of pneumonic infection for five months to six years, in some instances followed by emphysema. The cysts did not disappear under antibiotic treatment and required excision.

CASE IV. S. C., a 5 months old girl, was admitted to hospital on October 26, 1950, with a history of deep breathing since birth. She had not been cyanotic and had not had definite respiratory distress unil 6 days before admission, when she got a cold and began to cough. Her respirations then became labored, and, 2 days before admission, she became dyspneic and mildly cyanotic. She was treated elsewhere with steam, antibiotics and cough syrup, but did not respond. On her admission to the hospital, roentgenograms of the chest revealed loculated air pockets on the left side with herniation of the left lung to the right. The mediastinum was shifted to the right (Fig. 42). An emergency thoracotomy was done, and the left lower lobe con-

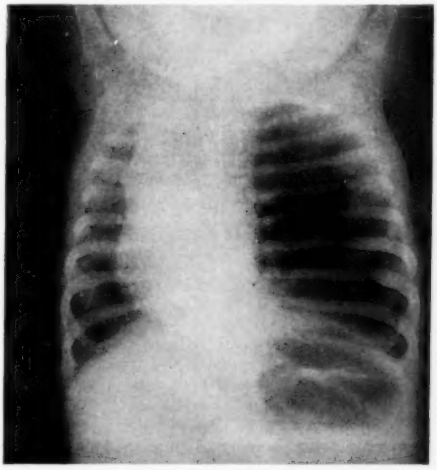

Fig. 42. Preoperative chest roentgenogram of a congenital lung cyst that presumably began to trap inspired air until it had enlarged to the point of endangering the patient's life. The overdistended left lower lobe cyst has compressed the left upper lobe and has shifted the mediastinum to the right, causing compression of the right lung.

taining a distended cyst was excised. The atelectatic left upper lobe expanded, and the mediastinum shifted to the midline. The patient's respiration improved. After an uneventful postoperative recovery she was discharged on November 7, 1950. Microscopic examination of the cyst wall showed that it was lined with ciliated columnar and cuboidal epithelium.

In sharp contrast to patients having congenital lung cysts are the infants with tension cavities that follow staphylococcal pneumonia. Surgical ex-

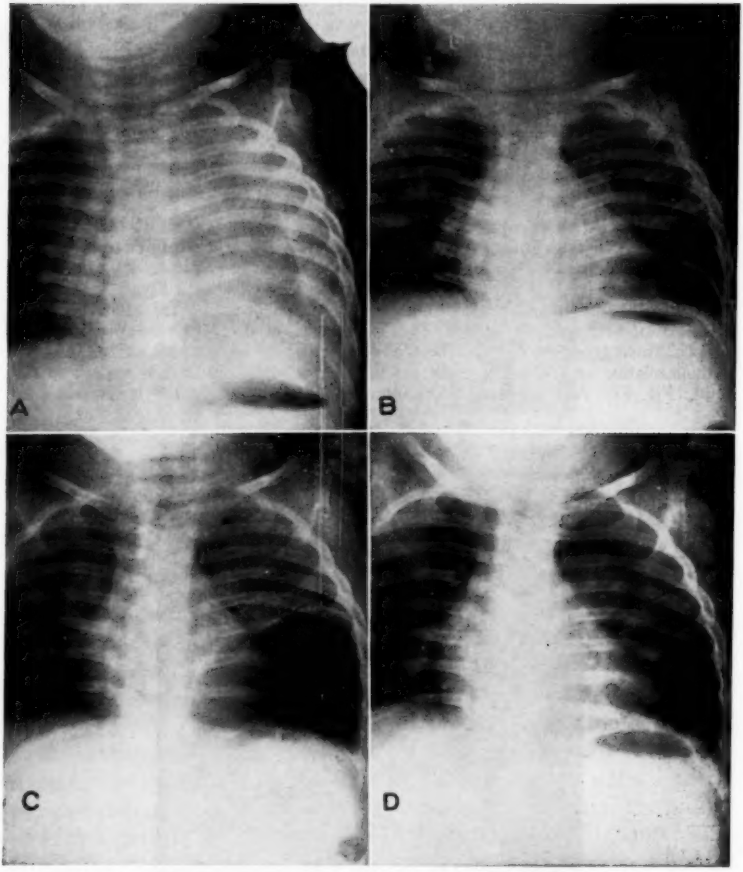

Fig. 43. Chest roentgenograms showing, *A*, pneumonitis of the left lung and left pleural effusion. *B*, The pleural effusion has been aspirated, and the left pneumonitis has almost entirely disappeared. However, two thin-walled cavities have appeared in the left lung base. *C*, Three months after the patient's discharge from the hospital the cystic areas in the left lung base have tripled in size. *D*, Five months after the patient's discharge from the hospital the cystic areas in the lung have disappeared spontaneously. This patient was not operated upon.

cision is contraindicated in the postpneumonic lesions, since they normally recede spontaneously.[2]

CASE V. C.B., a 6 months old girl, was admitted to hospital on November 27, 1951, with a history of rhinitis and cough for 2 weeks before admission. On November 25 she had fever of 105° F. The next day the temperature rose to 106° F., and she became lethargic and apathetic. On her admission to the hospital, resonance and breath sounds on the left side were markedly decreased. Roentgenograms demonstrated left upper lobe pneumonitis. The patient was treated with penicillin and Terramycin, but the pneumonitis spread to the left lower lobe. On November 30, 1951, a pleural effusion was noted (Fig. 43, *A*). Serous pleural fluid removed by thoracentesis was sterile. The patient responded to therapy, but two large thin-walled cavities appeared in the left lower lobe (Fig. 43, *B*). When the patient's fever and symptoms subsided, she was discharged to the chest clinic. The thin-walled cysts continued to enlarge until, 3 months later, they had tripled in size (Fig. 43, *C*). In 2 more months they had completely disappeared, and the patient has had no recurrence of symptoms (Fig. 43, *D*).

ATELECTASIS

Five patients had resection for atelectasis. The presence of atelectasis alone in the newborn is not an indication for pulmonary resection. With proper tracheobronchial aspiration and conservative management the majority of these patients will recover. In older children, however (ours were one to four years of age), atelectasis occurs following severe infection with enlargement of peribronchial lymph nodes and occlusion of the bronchus (middle lobe syndrome). It also may follow undetected aspiration of foreign bodies or may be the result of occlusion of the bronchus by nonspecific granuloma. Regardless of etiology, when atelectasis persists and the patient continues to have cough, fever, asthma, recurrent pneumonitis and other symptoms, the treatment of choice is surgical excision.

CASE VI. J.N., a 2 year old asthmatic boy, was first treated in the hospital in February, 1951, for left lower lobe pneumonia. After recovery he continued to have chronic cough with intermittent fever and recurrent acute follicular tonsillitis. He was readmitted on June 12, 1951, with pneumonia of the left upper and the right middle lobes. He was treated again with antibiotics and improved slowly. Bronchoscopic examination was done on June 18, 1951, and a large quantity of purulent material was aspirated. There was no evidence of compression or widening of the bronchi. The child was discharged on June 22, 1951.

On August 14, 1951, the patient had measles followed by recurrent respiratory infections and increased asthmatic wheezing. On December 19, 1951, the child again had right middle lobe pneumonia. The middle lobe remained atelectatic in spite of antibiotic therapy and bronchoscopic operation. Bronchogram demonstrated no bronchiectasis (Fig. 44). Finally, on June 13, 1952, a year and a half after the first attack of pneumonia, a thoracotomy was done. At operation it was noted that the bronchus to the right middle lobe was surrounded and occluded by enlarged peribronchial lymph nodes. The right middle lobe was removed. The patient had an uneventful postoperative course and has since been much improved.

MISCELLANEOUS

Infants and children are heirs to many diseases of the lung found in adults, plus a number of congenital anomalies which require surgical

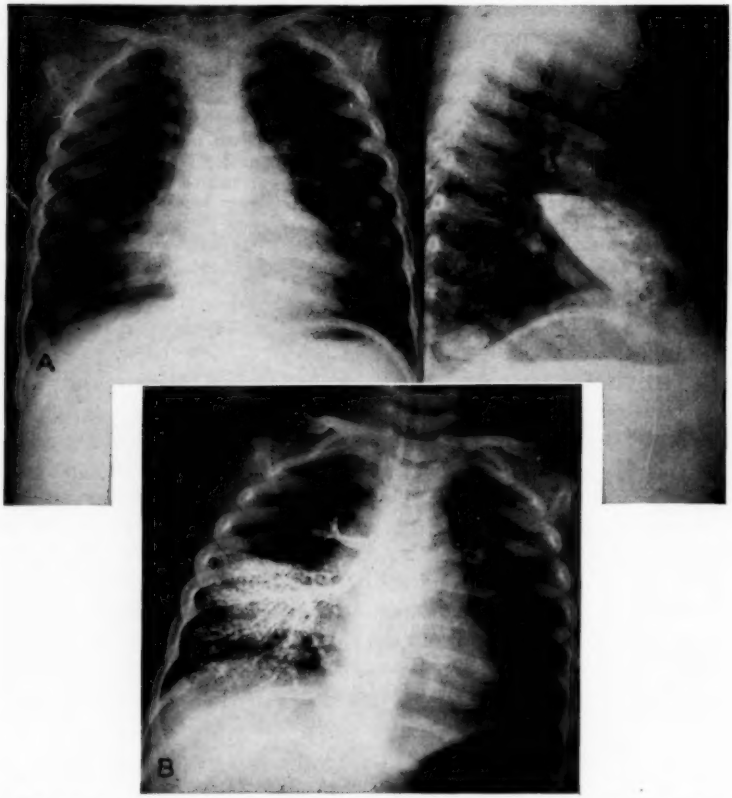

Fig. 44. A, Anteroposterior and lateral roentgenograms of the chest, demonstrating persistent atelectasis of the right middle lobe. *B*, Bronchogram reveals no bronchiectasis in the right middle lobe.

excision. Carcinoma of the lung has been reported in childhood, and pulmonary resection has been performed for residual secondary tuberculosis. A number of other unusual lesions have been reported. A complete survey of the literature is beyond the scope of this paper. Suffice it to say that the criteria for diagnosis and the principles of management are the same for children as for adults. In this series we encountered patients with pulmonary arteriovenous fistula, bronchial adenoma, bronchial dermoid cyst, and post-traumatic fracture of the main stem bronchus. The case of post-traumatic fracture of the main stem bronchus is of special interest and is presented in detail.

Case VII. B.J., a 5 year old girl, was admitted to hospital on October 27, 1947, with a history of having been involved in an automobile accident 3 years before

admission. She had sustained a fracture of the left clavicle and a left hemothorax which had not been completely evacuated. She had been asymptomatic until 3 weeks before admission except for increasing fatigability, cough and weakness. Percussion dullness was present, and breath sounds were decreased on the left. The apex beat of the heart was shifted to the left. Roentgenograms revealed collapse of the left lung with shift of the mediastinum to the left. Bronchoscopic examination and bronchograms demonstrated complete occlusion of the left main stem bronchus (Fig. 45). A thoracotomy was done on December 3, 1947. At the time of operation

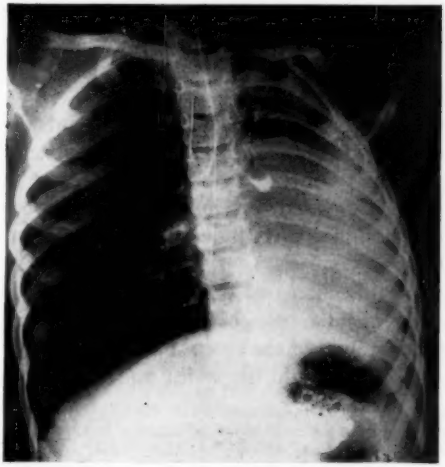

Fig. 45. Bronchogram demonstrating complete occlusion of the left main stem bronchus, distal to the carina. Note collapse of the left lung and shift of the mediastinum to the left.

the left main stem bronchus was found to have been completely severed, both ends having been closed by fibrosis. The lobes of the left lung were completely collapsed. It was interesting to note that there was no parenchymal suppuration, although the main stem bronchus had been occluded previously for over 3 years. The left lung was removed, and the patient had an uneventful postoperative recovery. She was discharged on December 13, 1947, and was followed up in the chest clinic until 1952. Postoperatively, her general condition improved. She had a satisfactory gain in weight, and her chronic cough and weakness ceased. She was able to engage in normal physical activity. No deformity of the thorax was observed.

COMPLICATIONS

There was no mortality in the series. The only serious complication was a case of temporary cardiac arrest which occurred during anesthetic induction before the proposed lobectomy was begun. The patient was successfully resuscitated, but had residual spastic paralysis. He is still recovering slowly, and resection remains to be done. Two patients with bronchiectasis, operated on before the advent of antibiotics, acquired postlobectomy empyema, but recovered after adequate drainage. Another

patient had chills and mild transitory hematuria following a transfusion reaction, but had no residual renal damage.

Pulmonary resection did not interfere with growth and development. As a matter of fact, in pulmonary lesions with chronic suppuration, growth and weight gain improved after excision of the offending lesions. There was no marked deformity of the dorsal spine or the thoracic cage following operation. The children tolerated loss of sizable portions of lung tissue without suffering impairment in exercise tolerance.[5, 8]

SUMMARY

1. Forty-four cases of pulmonary resection in infants and children are presented. Forty-two patients had total or partial lobectomies, and two had pneumonectomies. Thirteen resections were done as emergencies.

2. The diseases most frequently encountered were bronchiectasis, lobar emphysema, congenital lung cysts and atelectasis. Representative cases of each are described.

3. A number of miscellaneous diseases were noted, including pulmonary arteriovenous fistula, bronchial adenoma, bronchial dermoid cyst and post-traumatic fracture of the main stem bronchus.

4. There was no mortality in the series, and complications were relatively few.

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PUBLISHER'S FOREWORD TO "YOUR CHILD'S OPERATION"

Parents of a child who is about to undergo an operation are often at a loss what to tell the child beforehand, or worse still, they take the child to the hospital without any warning whatsoever. The psychic trauma resulting from this can be enormous. The child may lose faith in his parents; at the very least he may refuse to cooperate while in the hospital. The worries and nightmares that may follow an operation can produce mental distortions in the child that last a long ime or even forever.

Physicians must help the parents as well as the child and prepare them both for the coming ordeal. The busy practitioner may not have the time to explain in detail the various steps in hospitalization and operative procedures, nor is it desirable that he tell the child too much. The main purpose is to prepare him psychologically or to inform the parents so that they may undertake the child's mental preparation. The child needs reassurance. He needs to know that the separation from his parents, though necessary, will be short; that the people in the hospital, who will all be strangers to him and therefore perhaps frightening, really are going to "fix him up" or "make right" whatever is wrong with him; that when he comes home from the hospital he is going to be the same as he was before, except that what was wrong will then be right.

The material that follows was written for parents and children. The physician who has a child-patient who must have an operation may explain to the parents of the child whatever it is essential for them to know and emphasize the necessity of the child's confidence and cooperation. To help the parents prepare the child, he may give them the prose text of "Your Child's Operation." The verses and illustrations are to be given to the child only after he has had adequate mental preparation from both the physician and his parents.

It is hoped that this material may be of service to physicians and parents as well as children. Copies may be obtained by writing to the publisher and enclosing 20 cents for each reprint to cover cost of postage and handling charges. For lots in quantities the publisher will supply special prices.

YOUR CHILD'S OPERATION

BENNETT OLSHAKER, M.D.

How would you like to be taken from your home to a strange place where people you did not know would hurt you? Just the thought of it frightens us, but essentially that is what often happens to many of our children. To a youngster who has not been told beforehand, the trip to a hospital for an operation constitutes a strange and frightening experience.

Your physician has informed you that your son or daughter needs an operation. It is likely that your child has never had to be hospitalized before, and it is likely that this will not be the only hospitalization of his (or her) lifetime. Therefore it is extremely important that the child be prepared for this event so that he makes the best adjustment possible to it and to any future hospitalization.

Since the most common operation of childhood is the tonsillectomy, it has been chosen as the subject of this story.

What happens to a child who goes to the hospital for an operation? The parent and child arrive at the hospital, and from there on the procedure varies from one hospital to another. Usually they are interviewed by a receptionist as to name, address, age and other routine information (including perhaps his nickname, favorite toys, and the words he uses for routines such as toilet procedures). After this, laboratory work may be performed. This involves sticking the child's finger and withdrawing a few drops of blood. The young patient is then taken to his room or ward. Here he undresses and puts on hospital clothing or his own pajamas.

Certain routine procedures are then carried out: a nurse takes his temperature and pulse, an intern examines the patient, and in some instances an enema is given. For a period of time before the operation food

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is withheld from the child. In some hospitals preoperative medication may be given, and this may mean that the child will be given an injection.

Shortly before the scheduled time the child is taken to the part of the building where the operating suite is located. There, in a small room outside the operating room proper, an anesthetist administers the anesthetic. When the operation is completed, the patient is taken to a "recovery room" (or perhaps to his own room) until he awakens. Then he is put back into his own room, where he remains during his hospitalization. His throat feels sore, but when he has completely reacted from the anesthesia he is permitted to have cool drinks and, later on, ice cream. If all goes well, he probably will go home the next day. However, if he has a fever or there are other minor complications, he may have to remain a little longer.

Children have certain fears attached to the business of going away from home to the hospital. The younger children, and to some extent the older ones too, fear the separation from their parents and from the security the parents represent. Older children may fear the anesthesia and the operation itself. Some may misinterpret the operation and believe that it is in reality a punishment. Some may imagine that something has been done to their body while they were asleep and the damage would continue to increase after the operation is completed. Perhaps they bring to the hospital a not infrequent worry about some part of their body being hurt. They may believe that they are changed in such a way that they are not as they were before, or like the other children, and they are not able to do the things they previously did. These feelings, coupled with a lack of preparation of the child, may lead to evidence of emotional upsets—sometimes showing up in the form of persistent fears, uncomfortable habits, or changes in attitude or behavior.

It is important, therefore, that an attempt be made to prepare a youngster for the experience of going to the hospital for an operation. A child who knows what is going to happen may still have fear, but the fear will be much greater if he is led or tricked into a totally unfamiliar situation. The amount of preparation necessary will vary with the individual child. He should feel that the operation is a necessary thing, and this may best be done by talking it out or playing it out. The information should come, if possible, from someone the child relies on and trusts. For the very young patient a statement from the parent that the procedure should be done and the reassurance that everything will be all right may be all that is needed. The older child should be given more information about what will happen to him in the hospital. He may not be able to understand or utilize all the information, but he will have an idea of what is to happen to him. With the older child it would be a good idea to give him the information a week or two before the operation, permit him to talk over his fears, reassure him and correct any misconceptions about the antici-

pated event. Playing the situation out beforehand may be valuable. The child can be encouraged to go through the coming events step by step, using a doll or toy animal as the subject. In this way he may be able to express and get rid of some of his feelings about his coming operation. If a child desires to take some tangible object from home, a toy or article of clothing, he should be permitted to take it. In fact, it might be a good plan to give him an opportunity to take "a little bit of home" with him.

It is important to be truthful with your child. His questions should be answered to the best of your ability, and if you do not know the answers you might consult your physician to get the necessary factual information. On the whole, when given truthful information, youngsters will react adequately. It is sometimes helpful for the parent to be present when the patient has reacted from the anesthesia if conditions at your hospital permit it. If your child is the one who has to stay longer, explain why and tell him that he will go home as soon as the difficulty is corrected. Avoid the use of frightening terms when discussing the anticipated hospitalization with him.

In the story that follows we have tried to show what happens to a little boy who has a tonsillectomy. Most of the things that will happen to him are depicted, and you may supplement this with additional details. The story should help to familiarize the child with the sequence of events that will occur. He will see that Tommy did not mind the experience. He will know that his throat will be sore, but actually he will be no different from before. He will know that when the operation is over he will go home, but some children do have to stay a bit longer. And finally, before long he will be back doing the same things he did before.

The purpose of this children's story, then, is to furnish young patients, their parents, and other interested persons, a tool that may aid in making a forthcoming hospitalization more familiar and less frightening to the young patient. It would be advisable to find out in what ways the situation at your hospital will differ, explain to the child why you may not be with him at a certain point, and reassure him that you will visit him as soon as you are permitted to do so. Upon returning home from the hospital, permit the child to "talk over" how he felt about his experience, and attempt to correct any misconceptions he might have about what happened, especially to him.

On a street not far away
Little Tommy plays each day.
He likes to dress in cowboy suits
And wear his big, black western boots.

Once he made a trip downtown
To be seen by Doctor Brown.
The doctor said there was no doubt,
Tommy's tonsils should come out.

Tom went home to get things ready,
With the help of Brother Freddy,
Took pajamas, slippers too,
And a toothbrush, bright and new.

Then Tom, along with Mom and Pop,
Took a ride and made a stop
Beside a building, oh, so tall,
That had a sign upon the wall.

Together they all walked inside,
And took an elevator ride.
They rode up to the second floor,
Where Tommy's name was on the door.

He looked at Mom and said, "Oh, gee!
They've saved this room here just for me."
His mother helped him with his clothes
As he undressed from top to toes.

And soon a nurse with pretty hair
Came in to talk with Tommy there.
She said she came so she could see
Just what his temperature would be.

A friendly doctor dressed in white
Looked Tommy over with a light.
As doctor listened to his chest,
Why, Tom behaved his very best.

Tom didn't mind when he found out
There'd be one meal he'd do without.
He'd play with other girls and boys,
Or sit in bed and play with toys.

Now Mom took Tommy by the hand
And said to him, "You understand,
We'll be waiting here for you
When the doctor says he's through."

So with the nurse he walked away
To meet a man named Doctor Jay.
And Tom saw through an open door
The cap and mask the doctor wore.

The doctor showed him a machine
Like nothing he had ever seen.
It had a mask like pilots wear,
To breathe with, high up in the air.

For Tommy it was quite a treat
To use a mask that was so neat.
He breathed so very, very deep,
That he got tired and fell asleep.

He dreamed about the wild, wild West,–
Of all the cowboys, he was best.
He woke and saw the nurse and knew
That the doctor was all through.

Although his throat was feeling sore,
Tom was no different from before.
That night he had a happy treat,
All the ice cream he could eat.

When morning came, young Tommy dressed,
For he would now go home and rest.
Tom's little friend across the way
Had to stay an extra day.

Soon Tom was back in his own bed.
He played with Brother, and he said,
"Freddy, you can look and see,
I had my tonsillectomy."

Now on that street not far away
Little Tommy's back at play,
Dressed again in cowboy suits,
Wearing big black western boots.

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